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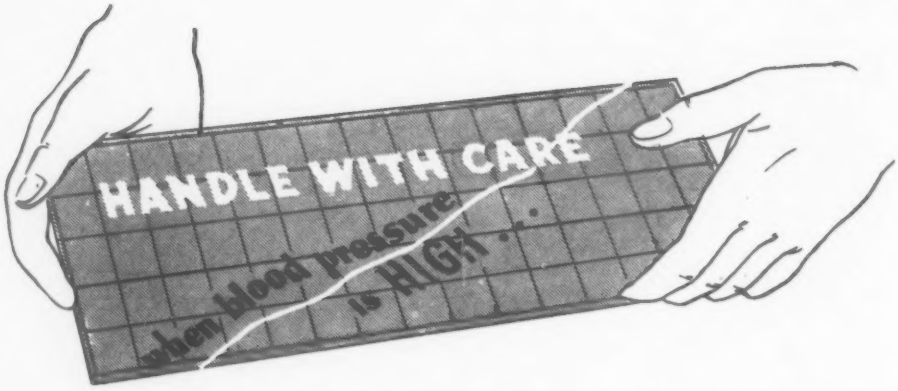

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THE AMERICAN JOURNAL
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ORIGINAL ARTICLES

THE RECOGNITION OF MENINGOCOCCIC INFECTIONS

By Paul S. Strong, Captain, M.C.
FT. EUSTIS, VA.

(From the Station Hospital)

The present day concept of the morbid processes involved in the pathogenesis of meningococcic meningitis grew out of observations made during World War I. During an epidemic at an Army Post, Herrick[3] was able to recognize about 45% of his cases in the premeningeal stage, and about 4% of these failed ultimately to show signs of meningeal involvement. The finding of the meningococcus in the blood stream of these early cases led him to describe the pathologic process as that of a primary sepsis followed in most, but not all instances, by a secondary meningeal localization. The path of infection of the meningococcus and the resistance of different individuals may be shown diagramatically as in Figure 1.

Meningococcal infection of the nasopharynx is probably of short duration and in the majority of cases produces few or no symptoms.[1,4] Long[5] believed that the high incidence of upper respiratory tract infections in his series of meningitis cases was probably a seasonal occurrence, because the majority of the cases occurred in a period when respiratory tract infections were common. The involvement of the blood stream is the earliest stage where significant recognizable symptoms occur. Hemorrhages into the skin, mucous or serous membranes are characteristic of meningococcal sepsis, but sufficient emphasis has not been placed on the diagnostic value of these lesions. It is possible that this may be due to the apparent infrequency with which the rash is encountered in interepidemic meningitis. Craster and Simon[2] stressed the importance of skin hemorrhages in meningococcic infections, stating that they are as specific for that condition as is the rash of measles or scarlet fever.* Describing an epidemic of meningococcic meningitis, Smithburn *et al.*[6] noted petechiæ in 68% of 144 cases. Herrick considered petechiæ to be of diagnostic value and noted the sign in about one-half of his cases. Of 92 cases which form the basis

* Hence the older use of the term "spotted fever," now wisely discarded as it was also used for typhus and Rocky Mountain spotted fever.—Editor.

of this report, 82% had petechiæ present either at the time of admission to the hospital or shortly thereafter.

It is our belief that the petechial rash occurs much more frequently in epidemic cases than has been reported in the literature. The reason for the failure to find the rash has probably been due to the lack of a careful search for it, to an error in calling the lesions capillary hemangiomata, or to the advanced stage of the disease process.

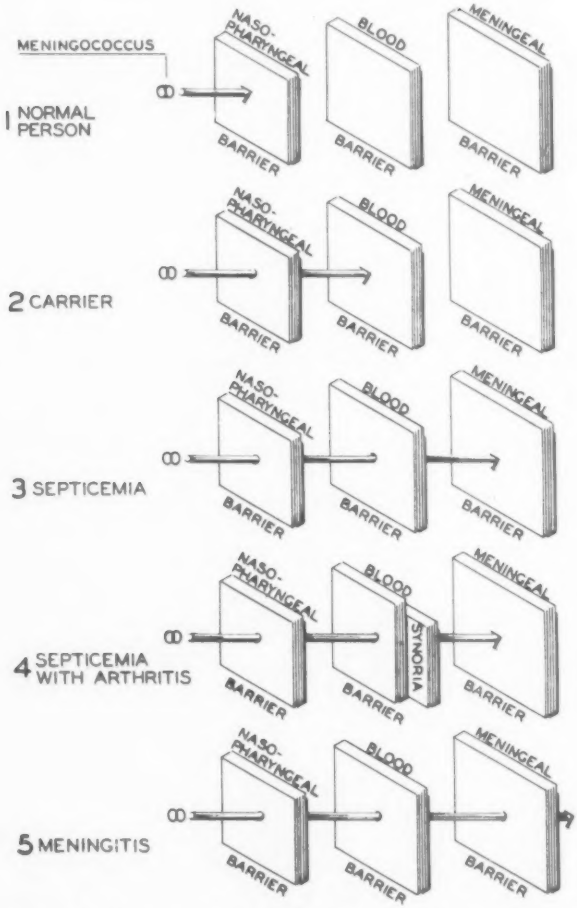

FIG. 1.—The path of infection of the meningococcus and the resistance offered by different individuals.

The specific rash of meningococcemia is always hemorrhagic (Fig. 2) and cannot be obliterated by pressure. A prodromal maculopapular rash may precede the petechial eruption but this is not characteristic. The eruption, if it is going to appear, invariably becomes manifest before the end of the first 24 hours of infection. Ordinarily, the rash is sparse and may be readily overlooked. The ankles and wrists probably

constitute the best locations to look for the rash as these areas are normally free of other types of skin eruptions. Any or all parts of the skin surface, the mucous or serous membranes may be involved. In our series, hemorrhages have been seen on the bridge of the nose; on the hard and soft palates; on the palms and soles; and in the con-

FIG. 2.—Petechiæ about the ankles of a soldier with meningococcemia.

junctivæ, in addition to the usual sites. Characteristically the rash reaches its full development within a few hours and fades rapidly, completely disappearing within a few days and leaving only a faint brownish discoloration of the skin. The lesions vary in size, shape and color. The majority of them are about 1 to 3 mm. in diameter, and range in shade from a rose color to a deep red. Not infrequently the

petechial spot is surrounded by a small red macule of a lighter color. In general, there should be no difficulty in differentiating these lesions from small capillary hemangiomata. In the very severe cases, purpuric spots (Fig. 3) or even large ecchymoses may accompany the petechiæ. These are usually of dark purple to blue-black color and vary considerably in size and shape. Although a widespread petechial and purpuric eruption usually occurs in the more severe cases, the absence of a rash does not necessarily indicate a mild case.

Rarely will the hemorrhagic form of measles be confused with meningococcemia, because the other associated clinical signs will make the diagnosis apparent. Typhus fever and Rocky Mountain spotted fever present a more difficult differential diagnosis. The severe meningococcemia may so closely simulate these two diseases as to be indistinguishable from them until meningeal signs become evident.

FIG. 3.—A large purpuric spot and several petechiæ on the dorsum of the foot of a soldier with meningococcic meningitis.

The other signs and symptoms of meningococcal sepsis, although less characteristic than the rash, are none the less important. The sudden onset of the disease, frequently in less than 6 hours, in an otherwise normal healthy individual, is an almost invariable feature of this type of infection. The chills, fever, drowsiness, headache, pallor, and pains in the limbs should suggest a blood stream infection. In many instances, the dissemination of the infection to the nervous system is so abrupt following the initial blood stream invasion, that a preliminary stage of sepsis fails of recognition. Signaling the spread of the infection to the nervous system are a series of signs and symptoms which hardly need enumeration. Perhaps the earliest sign is the severe intractable headache. In 99% of some 243 cases of meningococcal meningitis collected by the Surgeon General's office, headache was a primary and outstanding complaint. Of our cases, 94% have had this symptom as a chief complaint. The headache is generally felt all over

the head but is most severe in the frontal and occipital regions. Unrelieved by any form of treatment, including lumbar puncture, the headache has been justly described as "bursting." Vomiting occurs with more than average frequency. If present, it is very suggestive of central nervous system disease, especially when of a projectile nature. Disturbances of consciousness range from mild drowsiness to extreme coma. The drowsiness is not infrequently superseded by periods of marked irrationality. Other signs of meningeal irritation follow promptly, nuchal rigidity being the most readily recognized. The Kernig and Brudzinski signs soon become positive. Incontinence of urine and feces is common in the markedly irrational individuals. Rarely are the more advanced signs such as opisthotonus, and pareses of the cranial nerves seen because of the prompt administration of the sulfonamides.

Herpes simplex is frequently observed on the lips, nose, ears and back of the neck. This may occur any time after the 3d day and is seldom of any concern.

Of the 92 cases in this series, 30 were recognized before there were clinical signs of meningeal involvement. Spinal punctures were performed in 20 of these, and cells ranging in number from 8 to 27 were noted in 4 cases. Cultures of 3 of these fluids were positive for *Neisseria intracellularis*. Forty of the 90 blood cultures were positive for *Neisseria intracellularis*. Meningococci were grown from both the blood and spinal fluid in 23 instances. Seven cases of arthritis were encountered, 3 associated with meningeal involvement, and 4 without. The specific organism was grown from the synovial fluid in one patient with meningococcemia and arthritis, even though the blood culture was sterile.

Ability to diagnose meningococcic infections in the stage of sepsis will vary in different series of cases and in the same series of cases dependent upon: (*a*) the promptness with which medical care is sought; (*b*) the type and virulence of individual strains; and (*c*) the resistance offered by the nervous tissue of the individual. The history and physical findings alone should serve in establishing a diagnosis of meningococcemia and meningococcic meningitis. Laboratory confirmation should be sought in all instances, but treatment must not be withheld for this reason. Delay of 24 hours may mean the difference between treating a blood stream infection and a blood stream infection complicated by involvement of the central nervous system.

Summary and Conclusions. 1. An understanding of the pathogenesis of meningococcus meningitis is essential in order that the significance of its early signs may be appreciated.

2. Sufficient emphasis has not been placed upon the diagnostic value of the petechial rash in meningococcic infections.

3. Seventy-six out of 92 cases (82%) of meningococcic infections at this Post had petechial eruptions. In 5 instances a maculopapular rash was noted preceding the typical hemorrhagic eruption.

4. As the characteristic rash usually appears during the septicemic stage, its recognition will enable the early diagnosis of the disease.

5. In a number of instances the preliminary stage of sepsis may fail

detection as the dissemination of the infection into the nervous system is often very rapid.

6. Meningococcemia and meningococcic meningitis may occur in the absence of the characteristic rash.

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MENINGOCOCCEMIA

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During the past four decades at least 88 case reports of meningococcemia have appeared in the American and British literature. This clinical syndrome first described by Soloman[54] and subsequently by Herrick,[29] Dock,[19] Morgan,[40] Graves *et al.*,[25] Appelbaum[1] and others is characterized by a long-standing intermittent fever, cutaneous rash, arthralgia, myalgia, headache and the presence of the meningococcus in the blood stream. This paper is a clinical report of 3 new cases and an analysis of 85 cases collected from the literature that fall into the confines of the group of prolonged cases in which we are interested.

Pathogenesis. The clinical group of infections caused by the meningococcus has increased during the past half century, from a single clinical syndrome, meningitis, to several clinical entities. The carrier state, nasopharyngitis, endocarditis, arthritis, meningococcemia, in addition to meningitis, show the extent to which the various tissues of the body are susceptible to this organism. In spite of the attention paid to the discovery of the various infections caused by this organism, we are not yet in a position to set forth a complete story of the pathogenesis of meningococcal infections. The controversy still prevails regarding such a fundamental feature as the route of invasion. The "direct extentioners" and the "blood streamers" have not completely settled their differences. Finding the organism in the nasopharynx and in the exudate at the base of the brain led to the conclusion that the most direct route of entrance was along the nerves. Others[13] have demonstrated potential perineural pathways and by analogy with staphylococcal, streptococcal and pneumococcal meningitis following sinusitis have assumed the same chain of circumstances for meningococcal infections. There is some support for this idea in the report of

* Currently with the Coordinator of Inter-American Affairs, Division of Health and Sanitation, Washington, D. C.

Embleton[22] who found that 32 out of 34 persons dying of meningococcal meningitis had empyema of the sphenoidal sinus. In 3 of these instances the meningococcus was found in the bone.

As early as 1907, Flexner[23] noted that the same basal type of exudative process developed at the base of the brains of monkeys even though the meningococcus was introduced into the lower spinal canal. This fact led him to feel that the theory of direct extension was invalid if based on proximity alone. A few years later,[23] however, he favored the direct extension route. Elser and Huntoon[21] summarized the problem up to 1909 and concluded by supporting the blood streamers. Herrick[29] divided meningococcal sepsis into three stages: the local infection in the nasopharynx, the general invasion of the blood stream and finally the metastatic localization in the various organs of the body.

The usual narrow localization of the meningococcus on the posterior wall of the nasopharynx in the region of the pharyngeal tonsil has often been noted; the non-observance of this fact has caused many a carrier survey to fail. Buddingh[8] has admirably demonstrated the various stages of the meningococcal infection in the developing chick embryo. Virulent meningococci after being engulfed by white blood cells have been shown to cause phagocytolysis (breakdown of phagocytes) due to meningococcal toxins with subsequent liberation of the organisms.[42] These facts have caused us to reëxamine the mechanisms surrounding the portal of entry which might bear on the problem of the route of invasion.

The secretory activity of the mucous membranes tends to wash the organisms from the nasal cavity into the pharynx. If a foothold is gained in the region of the pharyngeal tonsil the organisms may cause a local inflammation and hyperemia. If they permeate the mucous membranes and enter the lymphatic system they will meet the lymph node barrier and eventually reach the superior vena cava. Should they be engulfed by the white cell phagocytes, often found on the outer surface of the mucous membrane, and phagocytolysis occur after the white cells have reached the blood, the living organisms would be virtually injected into the blood stream. There are no fluid drainage tracts which normally operate from the nasal cavity and especially the posterior nasopharynx directly into the central nervous system.

Furthermore there are many reports of recovery of the meningococcus from the blood before meningitis sets in, many also in which meningitis never occurs. In certain instances of fulminating infections a greater number of organisms have been found in the lateral ventricles of the brain than in the spinal fluid,[49] a fact not easy to explain if one believes in the direct extension theory. It has been shown that meningitis can be produced in rabbits by intravenous injections of meningococci following the production of hyperemia of the meninges[2] and also following spinal drainage.[62]

The gradual accumulation of experimental evidence may eventually settle this important problem. At the present time, however, in view of the uncertainties, one can only say it appears likely that the usual route of invasion is by way of the blood stream.

Case Reports. The introduction of chemotherapy has resulted in important changes in the methods of treating this type of infection. The following case reports illustrate certain aspects of chemotherapy in meningococcemia.

CASE 1. J. C., a 20 year old white Civilian Conservation Corps enrollee, was admitted to the Walter Reed General Hospital on March 21, 1939, with the complaint of intermittent chills, fever and general malaise of 2 weeks duration. This patient had had a generalized ichthyosis of moderate degree throughout his life. His past history was not important. No physical abnormalities were noted other than the ichthyosis simplex and a skin rash. Scattered over the arms, forearms, legs and thighs were pink maculopapular lesions about 1 cm. in diameter. These areas were tender and seemed to be more numerous on the parts of the body least affected by the ichthyosis. His blood culture was positive for Group I–III meningococcus 9 days after admission. Sulfapyridine was started at once and during the succeeding 11 days the patient was given 41.6 gm. He made a prompt recovery with no complications after an illness of 7 weeks. No change in the ichthyosis was noted as a result of the chemotherapy.

CASE 2. T. K., an 18 year old white Civilian Conservation Corps enrollee, was transferred from a civilian hospital to the Walter Reed General Hospital on February 17, 1939. One month prior to this date, the patient had been admitted to the civilian hospital with meningococcal meningitis. He was promptly treated with antimeningococcus serum with excellent results and prompt recovery. He was just about to be returned to duty when he began having joint pains, a low grade intermittent fever and a generalized rash "similar to insect bites." No other physical abnormalities were noted, the heart was normal and there were no murmurs. He presented no evidence of meningitis. Three successive blood cultures were positive for Group I–III meningococcus. He suffered daily temperature elevations with chills until 2 days after sulfanilamide was started when he became afebrile and made a prompt recovery. He received 37 gm. of sulfanilamide in 9 days. The duration of this patient's illness was approximately 7½ weeks.

CASE 3. W. P., a 17 year old white Civilian Conservation Corps enrollee, was admitted to the Walter Reed Hospital on June 7, 1938, with the complaint of a headache, fever and weakness of 2 weeks duration. It was learned that he had had meningococcic meningitis in February of 1938, was treated with serum and recovered without complication. He had enjoyed good health until 4 days prior to this when he complained of a fever and, for the first time, noted the presence of a macular rash.

Physical Examination. The patient was not acutely ill. The temperature was 98.8° F., the pulse rate 88 and the respiratory rate 20. His throat was injected and his tongue was coated. A red macular rash was observed on his feet, ankles, legs, thighs, buttocks and dorsum of the forearms. The early lesions were red, slightly elevated, round, regular, discrete and blanched on pressure. The older lesions were more elevated, had purple hemorrhagic centers which would not blanch on pressure. Some of the lesions were crusted. There were no scratch marks. The heart and lungs were normal. The blood pressure was 120 systolic and 68 diastolic. The spleen was not palpable and no other physical abnormalities were noted.

Laboratory Data. The initial blood examination showed 4.1 million red blood cells; 80% hemoglobin and 30,600 white blood cells (88% neutrophils). Blood Wassermann and Kahn reactions were negative. Agglutinations for Rocky Mountain spotted fever, brucellosis and tularemia were negative. A blood culture made on the 3d day, using an enriched medium, was strongly positive for Group II meningococcus. The first negative blood culture was obtained 19 days after admission.*

* Thanks are due to Dr. Sara E. Branham, of the National Institute of Health, Washington, D. C., for typing the meningococci recovered from these patients.

Course. The first 22 days of this patient's illness were characterized by daily paroxysms of fever, chills, crops of petechial spots and generalized arthralgia. Sulfanilamide in 1 gm. doses, 4 times a day, was started on the 4th hospital day and, though the patient continued to have fever, the rash disappeared until the 8th hospital day. He was desensitized to antimeningococcus serum and given 20 cc. intravenously. Additional serum was administered as indicated in Chart I but without beneficial results. Sulfanilamide was again tried in 25 gr. doses, 4 times a day for 4 days. The blood concentration reached 7 mg. per 100 cc. On the 4th day his red blood count had fallen to 2.7 million and the drug was discontinued. His temperature returned to normal on the 30th day of his illness and, after several weeks of convalescence he recovered without sequelæ. A total of 71 gm. of sulfanilamide and 195 cc. of antimeningococcus serum was used in the treatment of this patient.

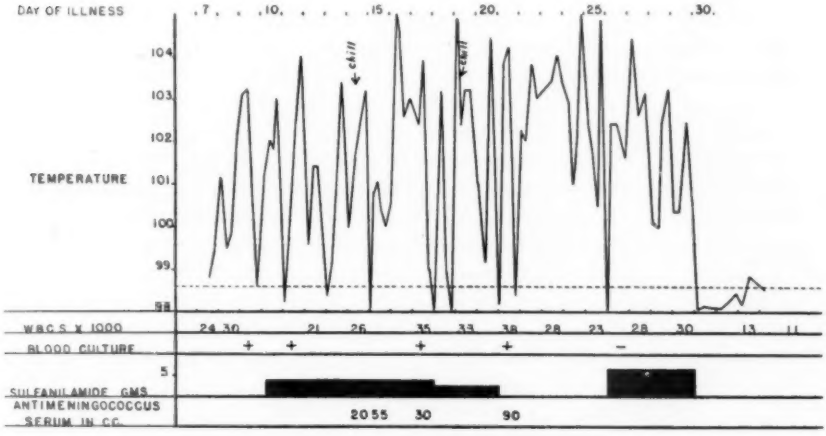

CHART I.—Case 3.

Clinical Characteristics of 88 Cases of Meningococcemia. This analysis of 88 cases, which includes the above 3 case reports, attempts to glean from the literature a more precise average clinical picture of this syndrome, as well as a better appreciation of some of its variations. Cases selected for this study were chosen on the basis of the prolonged course and the recovery of the meningococcus from the blood. There are a few reports in which the syndrome was identified after the eventual onset of meningitis and the subsequent recovery of the organism from the spinal fluid. In 3 cases described by Krumbhaar and Cloud,[32] and not included in this analysis, with sudden onset of meningitis, meningococci were isolated from the spinal fluid and meningococcic vegetative endocarditis was found at autopsy.

Of the 88 patients, 60 (69%) were males, 20 (33%) of whom were in the age group 20–29 years. The age distribution of 85 patients is presented in Table 1 using the age distribution of the population of the United States under 70 years for comparison. The exact age was not indicated in 3 case reports.

It will be observed that in the third decade the number of cases is nearly twice as great as one would expect. This difference is significant

and it might be interpreted to mean that persons in this age group are more liable to have meningococcemia than at any other age. This idea is strengthened by the fact that the two adjacent age groups also have higher relative incidences than might be expected. Nevertheless, I think this conclusion can only be advanced as a tentative one until more information is obtained.

TABLE 1.—AGE DISTRIBUTION OF 85 CASES OF MENINGOCOCCEMIA

Age groups	No. of cases	% of cases	% of U. S. population under 70—1930 census
0–9	8	9	20 3
10–19	19	22	19 8
20–29	27	32	17 4
30–39	15	18	15 4
40–49	12	14	12 7
50–59	3	4	8 9
60–69	1	1	5 5
Total	85	100	100 0

The duration of the illness from the onset of symptoms to cure was estimated in 80 case reports. The average duration was 11.2 weeks with extremes of 2 weeks and 120 weeks. In general, the younger the patient the shorter was the duration. An attempt to determine the seasonal prevalence of this disease was attended by little success. In 46 case reports the month and day of admission to the hospital were the only accurate dates obtainable, and if they are used the monthly prevalences are as follows: July, 7 cases; March and November, each 5 cases; January, February, June, September and December, each 4 cases; August and October, each 3 cases; May, 2 cases; and April, 1 case. It is to be noted that the duration of illness before admission to the hospital, the year of the attack, geographic location and the possible direct relation to epidemics of meningococcal meningitis were not taken into account.

TABLE 2.—FREQUENCY OF OCCURRENCE OF VARIOUS SIGNS AND SYMPTOMS IN 88 CASES OF MENINGOCOCCEMIA

	Male patients—60	Female patients—28	Total patients—88
1. Fever	57	25	82
2. Rash	53	25	78
3. Arthralgia	39	16	55
4. Chills	30	18	48
5. Headache	28	12	40
6. Myalgia	16	6	22
7. Arthritis	8	4	12
8. Vomiting	6	4	10
9. Palpable spleen	6	4	10
10. Sore throat	6	3	9
11. Sweating	7	2	9
12. Weakness	5	2	7
13. Herpes	4	1	5
14. Epistaxis	1	3	4

The frequency with which the various signs and symptoms occurred is shown in Table 2. Certain liberties were taken in the interpretation of a few reports. "Generalized aches and pains," for example, were

interpreted as arthralgia and myalgia in reports where these latter terms were not used. "Joint pain" was interpreted as arthralgia. "Swollen, tender joints," or "swollen joints" were classified as arthritis,[50] and tonsillitis or pharyngitis as sore throat.

Fever, rash, arthralgia, chills and headache constitute the five important features of this disease. Sore throat which might be expected to occur frequently, because of the portal of entry, was noted only 9 times. An enlarged spleen was recorded 10 times. The infrequent occurrence of herpes labialis was a bit surprising considering how often it occurs in acute meningococcal meningitis. Furthermore, 4 out of the 5 cases of herpes occurred in males, and all patients with this sign were in the third decade of life. In general, the frequency of occurrence of the subjective symptoms was lower in the first as compared with the later decades. Arthralgia, for example, was recorded only twice in 8 patients (28%) under 10 years of age, whereas it was noted 13 times in the 19 patients (68%) of the second decade.

In an earlier study[10] rash was noted as the most common feature. Several authors in the past 5 years have been specific in denying the presence of a rash. In 10 case reports out of the total (11.4%) there was no mention of a rash. This, I believe, is an important and encouraging change which supports the idea that blood cultures should be repeatedly made in all instances of obscure fever. As time advances it is conceivable that the symptom complex for meningococcemia will have rash in the third or fourth place.

The characteristics of the rash varied from a sparse petechial eruption to a diffuse one that commonly recurred in crops. The individual lesions varied in size from minute "flea bite" petechiæ to papules 1 to 2 cm. in diameter. White centers and subsequent suppuration were rarely noted. The most frequent lesion was a small pink papule with a red center located chiefly on the chest, arms and legs. The purpuric or suggillation type of rash so frequently seen in the fulminating types of meningococcal infection was not noted in the prolonged and chronic forms. Richter, Harrison and Abernethy, Brown[47] and Appelbaum[1] have published good photographic reproductions of the rash.

Generalized aches and pains in the joints and back are prominent features of this disease. Often these symptoms appeared only at the time the patient was having an elevation in his temperature, subsiding during the afebrile intervals. These symptoms occasionally caused the physicians to make an initial diagnosis of rheumatic fever, and salicylates were often given only to find that the fever was of an intermittent type even following the full doses ordinarily employed in rheumatic fever. In these reports a search for malaria plasmodia in the blood was frequently noted because of the similarity of the fever variations to a tertian or quartan type, and quinine was occasionally given on an empirical basis.

Meningitis occurred as a complication in 25 patients. A point of considerable importance is the relationship between meningitis and fatality. Riven and Applebaum[48] regarded meningitis as a bad prog-

nostic sign. Appelbaum[1] and Vesell and Barsky[60] were of the opinion that the presence of this complication does not make the outlook more serious. Chalier, Giraud and Morel[11] studied 27 cases of meningococcemia. In 8 cases without meningitis there were 4 deaths; in the remaining 19 cases with meningitis there occurred 6 deaths. They concluded that the localization in the meninges is favorable and helps the body to rid itself of the general infection. Among the 25 patients in the present report who developed meningitis there occurred 6 deaths; only 4 deaths occurring in the 63 patients without meningitis. This represents a statistically significant increase in the fatality in the meningitis group which fact would place some reliability upon the presence of this complication as an unfavorable prognostic sign. All patients developing meningitis who were over 39 years of age died (5 patients). Only 1 death occurred among the 20 patients with meningitis under 39 years of age (Table 3). It seems therefore that not only is meningitis a bad prognostic sign but the outlook is most serious when meningitis occurs in the older age groups. In 5 instances meningitis occurred before the prolonged meningococcemia set in. One patient had two separate attacks. Meningitis as a complication occurred most frequently between the 5th and 10th weeks of illness. Table 4 gives the frequency with which other complications occurred.

TABLE 3.—MENINGITIS OCCURRING AS A COMPLICATION IN 25 PATIENTS WITH MENINGOCOCCEMIA

Age groups	Male		Female		Total		Fatality (%)
	No.	Fatal	No.	Fatal	No.	Fatal	
0–9	0		2		2		0
10–19	2		1		3		0
20–29	10	1	2		12	1	8.3
30–39	2		1		3		0
40–49	2	2	2	2	4	4	100
50–59	1	1	0		1	1	100
Total	17	4	8	2	25	6	

Endocarditis was a complication which did not lend itself well to statistical study because of the indirect nature of the evidence presented as diagnostic of this condition. No uniformity of opinion exists as to the *in vivo* diagnosis of endocarditis caused by the meningococcus and postmortem evidence is scanty.[32] It seems most probable that the septicemic stage precedes both meningitis and endocarditis; consequently, in certain instances it is difficult to draw a line between the more characteristic cases of endocarditis and meningococcemia. It is believed that when vegetative endocarditis does set in as a complication of meningococcemia, the characteristic clinical picture of alternating periods of well-being with periods of indisposition, arthralgia and bouts of fever is changed. The patient whose condition is eventually proven to have been meningococcal endocarditis usually presents a symptom complex similar to the following: an intermittent fever which changes to a continuous one, this change being associated with the onset of weakness, loss of weight, congestive failure, cardiac incompetence, anemia and death.[32,46] In this group of 88 patients, 13 (15%) were

thought by their respective physicians to have had endocarditis, 4 of them died.[19,27,31] Necropsies were performed in 2 of these fatal instances and no endocarditis was found.[19,31]

TABLE 4.—FREQUENCY OF OCCURRENCE OF VARIOUS COMPLICATIONS AND ASSOCIATED CONDITIONS IN 88 CASES OF MENINGOCOCCEMIA

	Cases		Cases
Meningitis	25	Hemiplegia	1
Endocarditis	13	Thrombophlebitis	1
Nephritis	8	Jaundice	1
Anemia	6	Polycystic kidney	1
Pneumonia	2	Diabetes	1
Epididymitis	2	Congenital ichthyosis	1
Pericarditis	1	Banti's disease	1
Multiple abscesses	1	Conjunctivitis	1

Orgain and Poston[44] report an extraordinary coincidence of meningococcemia, pericarditis, pneumonia and thrombophlebitis in one patient. Two impacted wisdom teeth were extracted and this was followed by swelling of the neck and later fever and dull substernal pain. Sulfanilamide was administered with partial recovery until 15 days after the tooth extraction when the patient was readmitted to the hospital. Meningococci were recovered from his blood stream and pericardial fluid. He was treated with sulfanilamide and serum and after an illness lasting 68 days recovered without sequel.

Nephritis was reported in 8 patients, 5 of whom were in the first two decades of life. The nephritis was of the acute glomerular type. One patient[47b] died of nephritis 6 months after recovering from meningococcemia. The authors who reported this case believed there was some obscure causal relationship between the meningococcemia and nephritis. Anemia so frequently observed in other types of septicemia was noted only 6 times in this study and, in at least 1 of these 6, it was due to chemotherapy.

Heinle[27] describes the illness of 1 patient who had two well-defined and proven attacks of meningococcemia 2 years apart. This patient died in the second attack from "causes probably unrelated to the meningococcic septicemia." Cirrhosis of the liver, nephrosclerosis, bronchopneumonia and hemorrhage into the cerebellum were discovered at necropsy.

The treatment of meningococcemia has undergone important changes since the advent of chemotherapy. It is very difficult to make a true analysis of the curative effect of the various agents because of the tendency to use combined methods and also due to wide variations in amounts employed. Only those cases are being considered here in which no treatment, serum, or one of the sulfonamide derivatives was used. From Table 5 it will be seen that there is no significant difference between the no treatment group and the serum group. If, however, the serum group (46 cases) is compared with the whole chemotherapy group (14 cases) the difference in fatality is highly significant.

A total of 10 deaths (11%) occurred among the 88 patients. The 3 deaths not accounted for in Table 5 occurred as follows: 1 following treatment with antitoxin, sulfanilamide and blood transfusions;

another following the use of transfusions alone; the third after treatment with serum, emetine and mercurochrome. If the first death is credited to the chemotherapy group (15 cases) and the third credited to the serum group (47 cases) the difference in fatality is still significant.

TABLE 5.—RESULTS OF TREATMENT IN 68 PATIENTS WITH MENINGOCOCCEMIA

Method of treatment	Cases	Deaths	Fatality (%)
1. No therapeutic agent used	8	2	25.0
2. Serum alone	46	5	10.9
3. Sulfanilamide alone	6	0	
4. Sulfapyridine alone	7	0	
5. Sulfadiazine alone	1	0	
Total	68	7	

The 20 patients not included in Table 5 were treated with various combinations of the following therapeutic agents: antimeningococcal serum, antitoxin, blood transfusions, normal horse serum, autogenous vaccines, sulfanilamide, sulfapyridine, emetine, mercurochrome, hexamethylenamine, and fever therapy.

Reactions to antimeningococcal serum were frequent and in certain instances very severe. These reactions varied greatly from marked hypersensitivity to mild serum sickness. In several instances recovery seemed to follow the febrile reaction to the serum. Baehr's[3] patient had suffered from meningococcemia for 3 weeks. Immediately after the intravenous injection of 0.1 cc. of antimeningococcal serum the patient's temperature rose to 106.4° F., remained at this level for about an hour, and then returned to normal. The patient promptly recovered after this episode.

The average dose of selected therapeutic agents is given in Table 6. Vomiting complicated the treatment of 1 patient with sulfapyridine. An anemia resulted from the use of sulfanilamide in Case 3 above.

TABLE 6.—THE AMOUNT OF SELECTED THERAPEUTIC AGENTS USED IN THE TREATMENT OF MENINGOCOCCEMIA

Therapeutic agent	No. of patients	Average total dose	Extremes
1. Antimeningococcal serum	18	281 cc.	15–630 cc.
2. Sulfanilamide	5	56 gm.	16–148 gm.
3. Sulfapyridine*	3	26 gm.	16–34 gm.
4. Sulfadiazine	1	54 gm.	

* A fourth patient received 350 gm. of sulfapyridine.

The meningococcus was cultured from each of the 88 patients but not always without difficulty. Frequently several blood cultures were made before the organisms were recovered. With the steady improvement in our cultural methods as a result of a better understanding of the organism's growth requirement,[16] more and more cases are being diagnosed in the early stages. The organisms from 14 patients were typed, 6 were Group I–III and 7 were Group II–IV, 1 was described as of the "normal" type[38]—possibly, but not necessarily, Group I–III.

There are two important aids to the diagnosis of this condition. The first and most important is to think of meningococcemia whenever a patient presents a clinical picture characterized by prolonged inter-

mittent fever, rash, arthralgia, chills and headache. The second is the routine employment of frequent blood cultures made with enriched media.[16a] Stott and Copeman[57] state, "We believe that chronic meningococcal septicemia is so characteristic that bedside diagnosis is simple." Kennedy[31] makes the following observation: "Given a case of erythema nodosum, suspect meningococcus infection."

Summary. 1. As indicated by this analysis of 88 cases, meningococcemia is characterized by the following signs and symptoms in order of their frequency of occurrence: a long-standing intermittent fever, a polymorphous rash, arthralgia, chills and headache.

2. Meningitis occurring as a complication in meningococcemia, particularly in the older age groups, is associated with an increase in fatality and is believed to be a sign of bad prognosis.

3. The most favorable results from treatment were obtained by the use of chemotherapy.

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THE HYPERKINETIC DISEASES

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NOSOLOGICALLY, maladies in which the cause is reasonably clear may be broadly classified into five groups: (1) congenital abnormalities of tissue or of chemical metabolism; (2) diseases of endocrine origin; (3) the deficiency diseases; (4) others resulting from exogenous factors (something foreign, a toxin, a trauma, a bacterium, for instance, has invaded the organism resulting in disordered anatomy and function); (5) the hyperkinetic diseases which are predominantly endogenous in nature. In this group, the maladies arise largely conditioned by psychosomatic factors, the result of the impact of environmental influence upon a constitutional background. In these diseases there is a primary exaggeration of normal functions while marked anatomic changes follow. It has hitherto been difficult to recognize that disordered function may sometimes precede morphologic changes, because of the hitherto

domination of the Continental School which taught that morbid anatomy precedes changes in function. The concept of hyperkinesis is important for the interpretation and integration of a group of maladies whose etiology is conventionally regarded as uncertain or unknown. Furthermore, these diseases are increasing rapidly, as hospital morbidity statistics eloquently testify; and, because of their prolonged and recurring nature, contribute in a large measure to the increasing cost of sickness.

In order to elucidate this thesis, we shall consider some of the normal body functions and try to show how their exaggerated trends represent the dominant expression of certain well-recognized diseases and, how, with the initiation of the hyperkinesis, there results an orderly biologic progression of the disease from a larval to the fully fledged type.

1. *Normal Intra-arterial Pressure.* Its exaggerated phase is hypertension of the greater and pulmonary circulations. In this report we shall refer only to hypertension of the greater circulation. In a recent publication,[32] I discussed the currently recognized causes. These are arranged in what I regard as the order of frequency: (1) psychologic; (2) persistent Graves' syndrome; (3) renal; (4) adrenal blastomata or paraganglioma; (5) congenital peripheral resistances;* (6) increased intracranial pressure; (7) carotid sinus; (8) lead poisoning; (9) Cushing's syndrome; (10) obesity. Of these, all but the hypertension arising from the first two factors represent processes in which morbid anatomy precedes the exaggeration of function. In the first two, *i. e.*, hypertension of psychologic origin and that occasionally following persistent Graves' syndrome, the hypertension represents the primary process in the sense that it is the earliest clinical manifestation, so-called "essential" hypertension. Elsewhere[33] I have detailed the factors that condition the initiation. Physically, hypertensive individuals tend to be soft muscled, unathletic in type and bodily movement, pudgy, short-necked, ungraceful and overweight. There is a definite relation between obesity and hypertension.[17] Psychically, they are the antithesis of the child in mental makeup. They do not play, they are irritable and have single-track minds without avocations. While their mental horizon is narrow, within this range they are tense and pursue their aims with a grim desperation. That heredity is a factor in the production of hypertension has been well attested,[40,51] but in how far the hypertensive constitution is genotypic or phenotypic is still problematical. No one can deny that there has been a definite increase in essential hypertension in recent decades, as the present appalling mortality from the cardiovascular-renal syndrome testifies. I have elsewhere[33] discussed the influences that have brought about this increase. Briefly, I believe they may be explained, at least in part, as a by-product of modern civilization, of the stresses and strains that modern living entails. Testimony for this statement is the strik-

* The use of this phrase having been questioned, the author replies: "I purposely used the term congenital to include the cases of congenital stenosis of the aortic isthmus."—EDITOR.

ing increase in modern times of hypertensive disease in the northern negro,[25] whereas in his native habitat in the heart of Africa, hypertension is unknown.[15] It probably is not diet, because diet, except in so far as it is high caloric, does not induce hypertension. Moreover, the diet of northern negroes has not changed. It cannot be climate because this has not varied. I suspect that the reason may be industrialization and the competitive forces of modern civilization.

In other words, essential hypertension of the greater circulation, like infection and other disease conditions, is the resultant of a background and an insult. Either factor alone is insufficient.

The ultimate anatomic consequences of essential hypertension of the greater circulation are familiar—arteriosclerosis and eventually the catastrophic evidences of the cardiovascular-renal syndrome. The sequential relation of hypertension to arteriosclerosis and its attendant anatomic phenomena has been questioned, because the decrescent or senile type of arteriosclerosis occurs even without hypertension. These observers forget that hypertension is not an absolute but a relative value and that it is merely an exaggeration of the normal intravascular tension which by itself, given sufficient time, will produce arteriosclerosis. The evidence for this point of view lies, as I have pointed out,[34] in the independence in incidence between arteriosclerosis of the greater and lesser circulation. Gross arteriosclerosis of the pulmonary artery occurs almost exclusively in conditions in which a hypertension of the pulmonary circuit can be predicated, such as mitral disease, emphysema, etc. Now inasmuch as the normal pulmonary pressure is only one-sixth that of the aorta, the probability is very strong that even under extreme conditions, the pressure in the pulmonary circuit never approaches the normal pressure in the systemic circuit. The conclusion is obvious that if pressures less than the normal aortic pressure can produce arteriosclerosis in the pulmonary circulation, the normal systemic pressure, given sufficient time, can produce the decrescent or senile type of arteriosclerosis of the greater circulation. The following equation was therefore suggested to cover some of the factors: arteriosclerosis = intravascular pressure $\times$ time. There are, it is true, secondary conditioning factors involved in the genesis of arteriosclerosis, for instance, the chemical composition of the blood, the vascular supply of the walls of the vessels, intravascular stresses and perivascular resistance;[32] but these factors merely modify the lesion and affect its distribution. Apparently, normal intravascular pressure is the only normal function that has been shown to give rise to anatomic and sometimes to actual clinical disease. In this sense, arteriosclerosis (at least anatomic but not necessarily clinical) is the inevitable destiny of all animals who have a vascular system such as our own (Chart 1).

This chart explains why visceral arteriosclerosis even though patchy in its distribution is only exceptionally single in its clinical manifestations.

Inasmuch as the principal process disturbed in Graves' disease is the basal metabolic rate, we shall discuss the syndrome more fully under that functional heading. At this time, we need only point out

that hypertension of the greater circulation is one of the possible sequences of uncured or spent Graves' syndrome. In the earliest phases, the systolic pressure is usually elevated with a low diastolic pressure, probably due to the shunt engendered by the enormous increase in vascularity of the thyroid gland.[7] If the malady persists, these pressures no longer are labile and become more or less fixed. Eventually, both systolic and diastolic pressures rise and, in the course of many years, the cardiovascular-renal syndrome arises in one or more of its manifestations. It has been my fortune to have observed this sequence of events in a considerable number of instances, especially in older patients afflicted with persistent Graves' disease. Page[41] describes a syndrome, usually occurring in young women with essential hypertension, characterized by a high-strung temperament, tremor, tachycardia, perspiration, slight enlargement of the thyroid gland, sensitivity to cold and a slightly elevated basal metabolism, which he believes is due to diencephalic stimulation. His description certainly fits that of Graves' syndrome and I suspect that this disease is the cause of their hypertension. Inasmuch as I have tried to show (*r. i.*) that Graves' disease is largely a personality disease, the psychogenic origin of some cases of essential hypertension cannot be ignored. The fact remains that Graves' disease may occasionally be followed by the same clinical sequelæ as those of essential hypertension.

CHART 1.—POSSIBLE ANATOMIC AND CLINICAL SEQUENCES

Normal tension Hypertension	Arterio-sclerosis	Brain (cerebral arteriosclerosis; apoplexy). Retina: retinopathy. Heart: coronary disease; arteriosclerotic valvular disease; myocardial insufficiency Pancreas: capillary fibrosis of islands of Langerhans (diabetes). Splanchnic arteriocapillary fibrosis. Kidney: arteriocapillary fibrosis; nephrosclerosis. Extremities: arteriosclerotic gangrene. General arteriosclerosis; cachexia; atrophy.

2. *Basal Metabolic Rate.* The disease in which hyperkinesis, *i. e.*, increased basal metabolic rate, is a dominant expression is Graves' disease.

In a previous paper[35] I tried to show that Graves' disease is not a nosologic entity in the sense that it has a consistent background in morbid anatomy and a clear etiology, but rather a series of disorders arranged in a biologic progression that have received different eponyms in the past. The natural history of the disease usually extends over a long period. The earliest phase has been called Basedowid, autonomic imbalance, pre-Basedow, neurocirculatory asthenia,* etc. The middle

* There has been much debate whether "neurocirculatory asthenia" is the earliest stage of Graves' syndrome. We have records of at least a dozen cases at the Mt. Sinai Hospital where at first admission the diagnosis of neurocirculatory asthenia was made, and at second admission Graves' syndrome, in both instances on conventionally recognized criteria. Furthermore, on regression of the Graves' syndrome, a residuum of signs and symptoms often persists that is indistinguishable from neurocirculatory asthenia. As this exposition proceeds, we shall see the close relation of both to states of fear, whether in war or civil life. In a subsequent communication this topic will be discussed more fully.

stage has been termed "formes frustes," while the final stage is that conventionally termed "Graves' disease" with the characteristic quadrad of symptoms, *i. e.*, tremor, tachycardia, enlarged thyroid gland and exophthalmos, plus an elevated basal metabolic rate. Between the larval and the final florid form, one finds various combinations of signs and symptoms. For these reasons, the term "Graves' syndrome" is regarded as preferable. The proof of this statement lies in the fact that not only are such forward transitions frequently observed but, more frequently, regressions to the larval phases under the influences of either spontaneous remissions or of treatment.

I believe it is a fallacy to regard hyperthyroidism, as measured by the basal metabolic rate, as synonymous with Graves' syndrome. Graves' syndrome contains many clinical elements that are not explainable by the elevated basal metabolism alone. To regard the measurement of the basal metabolic rate as the sole diagnostic test of Graves' syndrome is arbitrary and not warranted by clinical facts for the following reasons: (1) Patients with so-called "spent" or "burnt out" Graves' syndrome who reveal the typical quadrad of signs may possess a basal metabolic rate within the normal range. (2) After a subtotal thyroidectomy which usually reduces the basal metabolic rate to normal, many of the clinical manifestations may persist for years, even though the patient is economically and perhaps socially restored.* (3) During the larval phases the basal metabolic rate is usually normal; but when, under the influence of an emotional strain, the disease assumes the florid form with a rise in the basal metabolic rate, are we justified in saying that a different disease has been born? All we may say is that hyperthyroidism has entered the picture. (4) The administration of toxic doses of thyroid gland mimics but by no means completes the clinical picture of Graves' syndrome. There is elevation of the basal metabolic rate, tremor and tachycardia and perhaps loss of weight but no exophthalmos or swelling of the gland. (5) Cases with clinical evidences of Graves' syndrome associated with myxedema occur rarely.[30] These mostly represent exhaustion phenomena. Hyperthyroidism as measured by the basal metabolic rate may be regarded as a sign, probably the most important of Graves' syndrome and as a measure of the activity of the disease, comparable to fever in infections. When the temperature of a patient with typhoid fever returns to normal, he has not necessarily lost his disease.

The common denominator in these various phases is a characteristic personality. In no disease that I am aware of is the personality so indissolubly bound with the clinical manifestations as in Graves' syndrome.

If the patient has been well observed before the onset of the disease or if his personality is reconstructed afterward, he will be found to conform to a vast race that may be described in general as the sensitive,

* It is occasionally an exceedingly difficult problem to estimate what is meant by "cure" in Graves' syndrome. In my experience, it is exceptional to get a complete *restitutio ad integram* in this disease. One or a number of the original quadrad of signs and symptoms usually persist.

emotional type; furthermore, this personality persists no matter what treatment is instituted, although clinical evidences of the disease have been eliminated. I regard the personality of the patient with Graves' syndrome as so characteristic that, in doubtful cases, the elucidation of the personality serves as a diagnostic measure. Phlegm and Graves' syndrome are, in my experience, antagonistic. Occasionally, one observes patients who appear to have a phlegmatic temperament but when one digs deeper, one finds that it is only a mask.

There are no anthropologic signs that are characteristic of the disease. However, in the constitutional phase these patients present, as a rule, a number of physical signs which represent the larval phases of the future characteristic quadrad of signs. Their eyes stare and are bright and they show more of the whites, especially in action or under emotional stress. During emotion, also, the pulse rate rises to excessive heights and there is tremor. In women, the neck tends to be fuller than normal and under emotional strain, especially during menstruation, when women are usually more touchy, they confess that their throats are larger. Their basal metabolic rate while within the normal range, usually, in my experience, veers to the plus side. Dermographia is nearly always present. These people are exceedingly touchy and respond to their environment like an Æolian harp. A look or harsh word upsets them easily and often irretrievably. As a consequence, they are usually intolerant. They are shy and introvert and live a life of escape. Their personalities have an unusual manic-depressive trend, sometimes even to the edge of a psychosis. They are quick in their movements and mental process. They are prolific day dreamers and idealism plays a large rôle in their mental life. They show a leaning toward the mystic and reveal the artistic temperament, so that in this group one frequently finds poets, writers, painters. Charm is a salient characteristic. They are usually bad sleepers. In my experience, they respond badly to thyroid preparations as opposed to those of phlegmatic temperament. They commonly relate that in their childhood a nervous disorder followed a slight emotional upset, such as a recitation or school examination. They tire easily mentally and physically. They are sensualists and live on stimulation, emotional, physical and even chemical. They easily become drunkards or drug addicts; indeed, suicides are by no means uncommon. These patients belong to what Kretschmer calls the "cyclothymic" constitution.

In no disease is a study of the immediate family so illuminating. The same malady afflicts two or more members of the family more than the normal law of averages allows and, what is particularly significant, few of the siblings are adjusted and phlegmatic. Most suffer from various forms of neuroses, and manic-depressive trends are common.[6] In how far these tendencies are genotypic or phenotypic, I am not prepared to say but from the study of numerous families, I believe that environmental influences, especially overprotection, play the dominant rôle.

In the majority of instances, the onset of the fully fledged disease is

ushered in by a psychic insult for which the patient was more or less unprepared, for instance, a robbery, a fire, the death of a close relative, an unrequited love affair, a terrible confinement, a frightful sexual episode, a sudden economic loss, an unwanted pregnancy, are some of the insults that I recall. There was a sudden crop of cases of Graves' syndrome in Vienna after the theatre fire horror in 1884 and in San Francisco after the earthquake. We have been particularly struck in the Mt. Sinai Hospital with the frequency of Graves' syndrome in German refugees, so that the term "Hitler Graves" has come into vogue. The essential ingredient in this insult is fear. Less often, the disease arises from slow and reiterated insults and the transition between health and disease is indefinable. At times after a sudden shock, the malady reaches its fruition even within a few days.

If the opportunity arises to observe the development of the malady in a person whom the physician has previously known, he will note that the disease represents an exaggeration and fixation of previous trends. A pulse that was normally fast, especially under an emotional stimulus, beats faster. The wide eyes become exophthalmic; a tremor which was previously noted only under excitement becomes exaggerated and constant and the previous emotionalism and instability of temperament is intensified. The basal metabolic rate is now definitely elevated.

This sensitive, emotional personality accounts for a number of things that have interested students of the disease: (1) The greater preponderance of Graves' syndrome in the female. (2) The rarity of the disease in children, in whom the subtler emotive powers are not fully developed. (3) The rarity of the disease in primitive races or in those of crude fiber. As in hypertensive disease, there has been in our experience at the Mt. Sinai Hospital, a decided increase of the disease in northern negroes since they became sensitized by contact with the white race. (4) The rapid increase in Graves' disease in recent decades owing to the increased "strain of living," the resultant of increased protective mechanisms.[36]

The psychogenic background of Graves' syndrome also explains the freedom of the lower animals from this disease because civilization has not affected them. Indeed, the complete disease cannot be experimentally reproduced—only individual signs and symptoms. The instances in which it has been reported are of doubtful validity. Graves' syndrome is essentially a human disease and especially one of the higher civilizations.

Some years ago, Lorand and Moschcowitz[28] published a psychoanalytic interpretation of Graves' syndrome. They found that: "already in childhood their adjustment to the members of their family was unsuccessful. On the one side they were too much pampered by the parents, especially by the mother, and on the other side, too great a demand was put upon them in the course of their development to which they could not adjust themselves as a result of their earlier protective environment. The vast majority of such patients may be said to have been sensitized to life. They were so shielded in their

childhood that when they reached adult age they could not face the conventional tribulations of every-day life with equanimity. They had difficulty in making decisions upon ordinary matters and were infantile in their reaction to life. There was a continual escape from every-day realities and, in consequence, these people would aver that their life had been an unusually hard one. The relation in childhood to the siblings as illustrated in certain cases is even carried over to adult life; for instance, the older sister replaces the father or mother to the other children. In their adult environment they showed the same type of emotional reactions to the attachments and frustrations as they did in childhood. Sexual difficulties, degrees of maladjustment, frigidity in women, fear of pregnancy and fear of childbirth combined with intense resentment and repressed aggression against men were present in all the patients. The unmarried girls showed a type which we can describe as psychosexual infantilism. Their childish attitude about sex matters, their more or less abnormal reactions and feelings concerning their menses, their attitude concerning marriage and sex in general lack all the judgment of the normal adult.

"Their relation and their reactions to their employers show an exact parallelism to their early reactions to their parents. The traces of their earlier emotional fixation to the parents were so obvious in their adult attitude to society that it could not be overlooked.

"In the male patients, whether married or unmarried, the same situations exist. Degrees of sexual impotentia, or at least difficulties in their sexual adjustment, were always present. The masturbation of puberty was continued by some of them up to marriage, partially on account of fear concerning sexual infection and partially as a result of their difficulties in their adjustment to the other sex. Coitus interruptus in the married patients was practiced for a long period of time to meet the demands of their wives in order to prevent impregnation, and at the same time, this sexual dissatisfaction caused resentment against the sexual partner. It then resulted in a tendency to stay away from intercourse or a strong drive toward unfaithfulness, with implications of fear and feelings of guilt."

The recognition of the individual and his environment is fundamental in the therapy of the disease. The human equation remains no matter what therapy is undertaken, and the impact of the two constitute a potential for a recurrence of the disease. It is futile to discharge a patient after a subtotal thyroidectomy without taking into consideration the ability of the patient to meet the ordinary stresses of every-day life and the environment to which he returns. Indeed, the lesson taught by these recurrences is that the treatment of the patient begins only when the operation has been finished. Although the constitution and the environment appear essential in the mechanism of production of Graves' syndrome, there must be another factor or at least a compensating mechanism, for the reason that sometimes one observes patients in whom despite the presence of both these factors, a Graves' syndrome did not develop.

When the disease is full blown to the stage of so-called toxic goiter

and continues more or less fixed, there may be a number of eventualities. We have already referred to the possibility of a progressive hypertension and its potentialities. In addition, the persistent tachycardia or the onset of a cardiac arrhythmia, especially auricular fibrillation, may result in myocardial insufficiency. Finally, of course, the disease may lead to death with the symptoms of acute thyrotoxicosis, namely, tachycardia, vomiting, diarrhea, progressive elevation of bodily temperature, emaciation and acidosis.

CHART 2.—CLINICAL EVALUATION OF GRAVES' SYNDROME

Constitution → formes fruste → Graves' syndrome	Persistent tachycardia Arrhythmia; auricular fibrillation	→Myocardial insufficiency
	Hypertension Acute thyrotoxicosis	See Chart 1

Synonyms: Basedowid. Autonomic imbalance. Pre-Basedowid.

3. *Normal Gastric Acid and Secretion.* The exaggerated phase is hypersecretion and hyperchlorhydria. The disease in which hyperchlorhydria is most often associated is peptic ulcer.

The cause or causes of peptic ulcer are obscure, but the view is steadily gaining ground that in the background is a constitution that represents a combination of physical and psychogenic characters. The physical characters have been described by Draper.[16] They have the "lean and hungry look" of Cassius, the expression is hard and tense, the eyes deep and sullen, the lines of the face are sharply drawn, the mouth is firm, the jaws sharply angled and the masseter muscles are prominent. These patients are usually cyanotic and show a tendency to erythremia. To what extent these physical characters are phenotypic or genotypic is as yet impossible to estimate.

Psychologically, in my experience, the vast majority of ulcer folk conform to a certain type of personality. They are intolerant, all or nothing, self-absorbed and mentally inelastic folk with strong aggressive, masochistic and sadistic tendencies. They harbor strong grudges and it takes them long to overcome any emotional strain. Even their humor is sadistic. They have a paranoid trend. They are haters and fighters.

As in Graves' syndrome, one finds with remarkable frequency that preceding the onset of the clinical symptoms, the patient passed through a period of emotional conflict; the illness or death of a relative, economic distress, the development of a powerful hate, etc. Whether this actually initiates the ulcer or merely activates it, is problematical; more likely, the psychologic insult induces activity. Clinicians have long recognized that a restful holiday can induce a remission even without the conventional dietary regimen. It has been my experience that when a patient is resistant to the Sippy treatment, he is often in a state of mental upheaval; when this is corrected, the symptoms promptly abate.

Indeed, so strong are the interweavings between the psyche and peptic ulcer that a considerable lore has accumulated on the psycho-

genic origin of peptic ulcer. I have summarized these views,[37] but the conclusions are diverse and conflicting. Experimentally, peptic ulcers analogous to those found in the human organism have been produced in animals but only by methods that do not obtain in human beings. Experimentally, the vast majority of observers have succeeded in producing only acute hemorrhagic erosions and because they show no tendency to be limited to the "pathway" and invariably heal promptly, it is unlikely that they represent the forerunners of the true human peptic ulcer. Indeed, the entire issue concerning the pathogenesis of peptic ulcer has been clouded by the uncritical acceptance of the hemorrhagic gastric erosion as the precursor of peptic ulcer. Hemorrhagic erosions are common phenomena at postmortem and are found in association with true peptic ulcer, in sepsis, in peritonitis following abdominal operations[19] in localized sclerosis of a gastric vessel, and following operations upon the brain,[13] but proof as yet is not forthcoming that these erosions, any more than the experimental variety, pass into the true Cruveilhier peptic ulcer. As Mann and Bollman[29] state bluntly, "If the mucosal lesion in man which precedes the development of the characteristic peptic ulcer begins as a hemorrhage into the mucosa, it appears that many of the results of our investigations (*v. i.*) would have little if any clinical bearing." Indeed, a considerable part of the experimental research concerning the problem of peptic ulcer has concerned itself with attempts to transform this acute hemorrhagic erosion into the chronic type; the results at best are equivocal. A few have succeeded but by means that are unphysiologic, for instance, by repeated Roentgen ray dosages or by injecting chemical irritants in the neighborhood of the ulcer.

The recent clinical and experimental observations of Bernheim and Penner[44] who showed that hemorrhagic erosions of the gastro-intestinal tract are commonly shock phenomena, have helped I believe to clarify considerably our knowledge of the causes of hemorrhagic erosion both in man and animals. Their observations certainly make one skeptical of the much quoted neurogenic theory of the origin of peptic ulcer sponsored by Cushing,[13] who found that *operations* on the brain were occasionally followed by a gastric erosion. Penner and Bernheim call attention to the frequency of shock after such operations, and in their analysis of postoperative hemorrhagic erosions they also found that shock was a common feature. This probably accounts also for some of the erosions found in association with peptic ulcer with fatal hematemesis (Moschcowitz, Mage and Kugel[38]). The association of true peptic ulcer with erosion does not necessarily justify the conclusion that the erosion was the precursor of the ulcer. In addition to the fact that it may be a shock phenomenon from severe hemorrhage, it may be the result of the associated mucosal inflammatory changes secondary to the peptic ulcer. In brief, no satisfactory evidence has been presented which shows that the hemorrhagic erosion is the earliest phase of peptic ulcer. Hauser,[21] who had spent a lifetime studying the genesis and pathology of chronic peptic ulcer, doubts this relationship.

The mechanism whereby the impact of psychologic influences upon a constitutional makeup is transformed into a peptic ulcer has been subject to considerable speculation. Part of the difficulty arises from the fact that, as opposed to hypertension and Graves' disease, we are not in the position to observe transitions, either clinically or in morbid anatomy. Hitherto, the stomach has been clinically an inaccessible organ, the only method of visualization being the Roentgen ray. This method is hardly satisfactory for the purpose of studying natural history because it only demonstrates an ulcer after it has matured. Serial gastroscopy offers a reasonable hope that the earliest lesion of peptic ulcer and its transition may eventually be demonstrated.

The only experimentally produced ulcers that correspond closely to those of the human were produced by Mann and Bollman.[29] These ulcers not only occurred exclusively in the "pathway" but grossly and histologically were identical with the true peptic ulcer. They obtained their results in dogs by elimination of the duodenum with the jejunum sewed to the pylorus. If the common bile duct and the pancreatic duct remained implanted into the duodenum, they obtained 20% ulcers; if these ducts were transplanted into the ileum, they obtained 50%. If the entire normal mechanism for receiving the gastric contents was eliminated by the functional resection of the duodenum together with the secretion poured into it by the second method, with anastomosis of the proximal end of the jejunum to the terminal ileum, they obtained 95% ulcers. The controlling factor is the acidity. In other words, these methods prevent the neutralization, dilution or buffering of the gastric contents as it passes the stomach. By repeatedly giving hydrochloric acid to normal dogs by continuous drip 8 hours each day, they obtained an ulcer in about 4 weeks. Daily repetition of excess acidity depresses the neutralizing ability. Such ulcers heal in a few days following discontinuance of the acid. In the type of ulcer obtained by elimination of the duodenum and its contents, the ulcer appears rapidly, in hours or less than a day. The morbid anatomy of the primary lesion as given by Mann and Bollman probably represents the prototype of that which, we predict, will eventually be found in the human stomach. "Macroscopically, they appeared as saucer-like depressions in the mucosa about 2 cm. distal to the pylorus. In their incipience, there is always a ring of mucosa between the ulcer and the pylorus. In the earliest stages, there is a small area covered with a homogeneous gray membrane. When the membrane is sponged off, a slight depression is uncovered where the surface of the mucosa had disappeared and which bled profusely. After the mucosa is eroded the process may proceed quickly until the wall is perforated. Microscopically, the gray membrane is composed of mucosal cell débris. In the earliest stages the injury involves only the tips of the tubules. Hemorrhage then occurs between the tubules underneath the gray covering. As more of the mucosa is injured, leukocytic infiltration occurs, the ulcer penetrates beneath the muscularis mucosa and the ulcer assumes the chronic type.[37] Mann and Bollman have apparently solved the problem of chronicity of peptic ulcers, because the agency

which prevents their healing persists. These experimental results prove, if nothing more, that the acid factor is vital in the production of ulcer. This has long been surmised clinically by a number of significant observations: (1) Reports of simultaneous association of peptic ulcer and anacidity are so rare that experienced observers like Palmer and Heinz[43] are skeptical that this association exists. (2) Recurrence of either peptic or jejunal ulcers following gastric resection does not result, at least in our experience at the Mt. Sinai Hospital, if complete anacidity is obtained. (3) In the rare cases of ulceration of Meckel's diverticulum, aberrant gastric mucosa is nearly always present and the ulcer is found in the intestinal and not in the gastric portion of the mucosa.[3] (4) Peptic ulcer was not found in association with achylia gastrica in over 800 cases of pernicious anemia.[26]

In how far do these observations apply to the psychogenic origin of peptic ulcer? In view of the importance of the acid factor, the question arises whether the hyperchlorhydria and hypersecretion so commonly associated with peptic ulcer, especially of the duodenal variety, precede or only follow the initiation of the defect. That emotion may produce temporary hyperchlorhydria is a well-established observation.* There are no data available which indubitably establish the presence of hyperchlorhydria in the human previous to the development of an ulcer, but in view of Mann and Bollman's work on the acid factor and the fact that psychic influences cause an increase in acidity and secretion, the probability is strong that continued or reiterated emotional strains do cause a sustained hyperchlorhydria and hypersecretion before the initiation of the ulcer. It seems highly probable therefore that hyperchlorhydria and/or hypersecretion represents one of the intermediary mechanisms between the psyche and the ulcer. In this connection, the experiments of Stahnke[48] and Silverman[47] are convincing. Stahnke showed in dogs that electric stimulation of the vagus nerve, 40 minutes daily for 2 to 3 months, resulted in marked increase in gastric acidity and peptic activity and, in some instances, a peptic ulcer followed. Silverman found that sham feeding through an esophagostomy opening in the neck caused a powerful stimulation of the peptic glands with large amounts of fluid of a high acid and peptic titre, and eventually the occasional appearance of a peptic ulcer.

Although the discussion in the two following paragraphs is not directly related to the hyperkinetic aspects of peptic ulcer, it is necessary because in many quarters such mechanisms are seriously considered and would tend to negate our thesis.

There is a widely prevalent view that part of the mechanism of the development of peptic ulcer is vascular by way of the vasomotor nerves causing spasms,[4,21,50] or by narrowing (arteriosclerotic ulcer). Considerable argument and experiment has been expended upon this phase

* In a recent publication, Hoelzel[22] who made daily observations upon his gastric acidity over a period of years, found that while he was passing through a period of fear owing to the anticipation of being shot, his acidity rose to appreciable heights. When he moved from his city so that the occasion for fear ceased, his acidity returned to normal.

of the problem, but it cannot be said that the results leave a sense of satisfaction. A vascular mechanism for the genesis of peptic ulcer will be difficult to maintain for the following reasons: (1) It is almost impossible to cause an infarct or necrosis in the stomach even by complete closure of a gastric vessel. This is manifest not only experimentally but also in human beings when it becomes necessary in the course of gastric operations to ligate numerous vessels. (2) There is no evidence that the sclerotic vessels so commonly found at the base of a peptic ulcer represent primary changes. They are probably secondary inflammatory lesions. Peptic ulcer is surely not a disease of the decrescent years when vascular occlusions in other parts of the body are common enough. (3) A vascular origin does not explain the remarkable predilection of peptic ulcer for the pathway and the upper duodenum. (4) If we accept the experimental ulcer of Mann and Bollman as the prototype of the human ulcer, there is nothing in their description of the pathogenesis of these ulcers that suggests a primary vascular mechanism. Indeed, as Palmer[42] points out, the fact that the lesion begins in the mucosa and not in the walls, speaks against a vascular mechanism.

Furthermore, the contention of Konjetsny and his school that a chronic gastritis precedes the development of a peptic ulcer must be viewed with much skepticism. Available evidence seems to show that in most instances the gastritis is secondary, the result of chronic infection from the ulcer. When a "gastritis" is present unassociated with ulcer, the histologic criteria, at least as far as I have observed, are remarkably indefinite both in regard to its status as a true inflammation and to its variations from the normal.* Other considerations aside, a primary gastritis does not explain the almost human character of peptic ulcer, its limited localization not only to the gastric and upper duodenal mucosa but more particularly, to the "pathway," its great preponderance in males and the rarity of the disease in childhood and in primitive peoples.[20] Even assuming that a gastritis may be the background, such an assumption adds nothing to the etiology of peptic ulcer, because the cause of the gastritis is still dark. The same processes of reasoning are applicable in relation to the problem as to whether bacteria, especially streptococci, are responsible for the lesion. In other words, every attempt to explain peptic ulcer as an infection has proven futile.

The relation of psychosomatic factors to the genesis and recurrence of peptic ulcers has significant implications not only on therapy but on prophylaxis. Hurst[23] has pointed out that peptic ulcer has taken the lead as the chief cause of medical disability in British and Canadian soldiers; and Crohn[11] believes, in view of Hurst's report and the rise of peptic ulcer in Finland, that we may expect a rise in the incidence of peptic ulcer in this country in the near future. It is our distinct

* It seems a remarkable fact that the normal histology of the stomach has not been sufficiently studied either in regard to normal deviations, age, the active or resting stage, character of nourishment, race, etc.

conviction that there has been an increase in evidence of peptic ulcer in the Mt. Sinai Hospital, especially since the depression of 1929.

As I pointed out some years ago[37] there is a remarkable parallelism between peptic ulcer and Graves' syndrome. In both there is a rather characteristic psychic background, although at times these backgrounds seem to overlap. In Graves' syndrome, the psyche is a highly sensitive and emotional one; in peptic ulcer it is rigid, aggressive and intolerant. In both, a latent malady is brought to light by emotion, either catastrophic or by slow reiterated insults. In both, it is sometimes exceedingly difficult to know when the disease actually begins, but whereas in Graves' syndrome, if one is fortunate, the observer can follow the intensification and increasing tempo of the signs and symptoms from the larval constitutional stage to the formes fruste and finally to the fully blown form, in peptic ulcer, owing to present diagnostic criteria, one can never be sure whether the previously existing chronic indigestion represented an actual ulcer or not. Strictly speaking, therefore, we do not yet know the preceding or intermediate stage of peptic ulcer.*

In both, recurrences are common and frequently these recurrences are preceded by emotional upset. In both, excess of normal function dominates the clinical expression of the disease; in both psychic rest is an important adjuvant in therapy, and in both, surgical intervention has parallel indications and results. In Graves' syndrome the operation aims at removing the hyperthyroid element; in peptic ulcer, the elimination of the hyperchlorhydria and the hypersecretion.

4. *Tonus of Cardiac Sphincter.* The increased phase of this tonus is represented in cardiospasm. That there is a normal cardiac sphincter has been demonstrated by Hurst,[24] who has coined the term "achalasia" for the persistence of the normal tone of this sphincter which fails to open before the normal peristaltic esophageal wave in the act of swallowing. Cardiospasm may be primary or secondary. Secondary cardiospasm follows various lesions, for instance gastric or esophageal ulcer, gall bladder disease, gastric and esophageal neoplasms, etc., but more often cardiospasm is primary. It is needless to enumerate the various causes of primary cardiospasm that have been submitted, because they have not been substantiated by adequate evidence. Most of the hypotheses implicate overstimulation of the vegetative nervous system, either physiologic or as the result of organic changes in the plexus of Auerbach embedded in the walls of the esophagus. The probability is indeed strong that the cardiospasm is mediated through the pathways of the vegetative nervous system, but this is a mechanism and not a cause. Furthermore, it is very probable that the organic degenerative changes witnessed in the Auerbach plexus are not primary but secondary to the ever-present inflammatory changes involving the coats of the esophagus in prolonged cardiospasm. In

* It should be strongly emphasized that clinical peptic ulcer and peptic ulcer of morbid anatomy are by no means synonymous. It has been shown time and again that peptic ulcer of even considerable dimensions may exist without any clinical evidences whatever. A recurrence of symptoms may not represent the formation of a new ulcer but the activation of a preëxisting one.

recent years, evidence has accumulated that primary cardiospasm is psychogenic in origin. The older textbooks all agree that cardiospasm usually occurs in psychoneurotics and that it frequently follows a psychologic trauma. Schindler[46] in his cases unearthed a history of deep anger a day or two before the onset of symptoms. Indeed, in the earliest phases of the cardiospasm he obtained a cure by psychotherapy or hypnosis. Alkan[2] found violent psychic excitement preceding the onset of symptoms. More recently, Winkelstein[54] reported 8 cases in all of which a psychologic trauma initiated the symptoms of cardiospasm.* In 2 of his cases, seen in the early phases, psychotherapy resulted in a cure. In the later phases when the cardiospasm is fixed and anatomic changes have occurred, both Winkelstein and Schindler agree that dilatation of the esophagus is essential.

The natural history of cardiospasm is fairly typical. In the early phases, the symptoms come and go with the intervals of well-being becoming progressively shorter. Eventually the difficulty in swallowing becomes constant, the dilatation and tortuosity of the esophagus become progressive and finally pronounced inflammatory and ulcerative lesions ensue with marked hypertrophy of the muscular coat. The intensification of the spasm and the presence of these organic changes account for the failure of psychotherapy in the terminal stages of cardiospasm.

Whether there is a constitutional factor or a characteristic psychologic pattern in patients with cardiospasm requires further observation.

5. *Tonicity, Peristalsis and Secretion of the Colon.* These three normal functions are grouped together because, as a rule, the clinical experiences consequent upon their hyperfunction are associated. The maladies in which these hyperfunctions predominate are mucous "colitis" and non-specific ulcerative colitis.

(*a*) *Mucous "Colitis."* For the following data I am largely indebted to the excellent comprehensive monograph of White, Cobb and Jones.[53] The term mucous "colitis" covers not only those conditions in which mucus is constantly passed but a number of conditions in which the passage of mucus is an occasional symptom. These have been described under the appellations of "irritable colon," "spastic constipation," "nervous diarrhea" and "alternating constipation and diarrhea." The malady occurs uncomplicated but is not infrequently associated with other psychosomatic disorders, such as the irritable heart of soldiers (neurocirculatory asthenia), asthma, Graves' syndrome and peptic ulcer. There is no crude correlation with any anthropomorphic type. The sigmoidoscopic picture, while not specific, reveals spasm, dilatation of the superficial venules, the presence of mucus and a somewhat granular appearance of the mucosa. The characteristic radiographic appearance of the colon reveals rapid filling, spasm and irritability, deep haustrations and the string sign. Little is known of its morbid anatomy because patients do not die of this disease. In

* In the discussion of Winkelstein's paper, Verbrycke referred to a physician who was cured of a cardiospasm by dilatation of the esophagus. He remained well for months but had a prompt recurrence when bandits robbed his bank.

one case of Mallory's, the goblet cells of the mucosa secreted a large amount of mucus. The patients often reveal vasomotor symptoms mediated through the autonomic nervous system, such as dilation of the pupils, ptyalism or aptyalism, sweating, exaggerated pilomotor responses, sighing respiration and sphincter response. They report that allergy was the cause in only about 4%. In the remainder, emotional tension, acute and chronic, was the cause. Psychologically, White, Cobb and Jones found that asthenia was common. There was high incidence of sexual indifference, two-thirds of the women were frigid and men were satisfied with infrequent intercourse. Minor compulsions existed in a large number—excessive neatness, meticulousness and overconscientiousness. True obsessions were not encountered. These patients ruminated on their problems. Phobias were common, especially of crowds, and they have depressive tendencies. The majority were dependent persons. The emotions most commonly associated were resentment, fear and guilt in that order. They showed difficulty in making decisions. White, Cobb and Jones report experiments in which changes simulating those seen in mucous colitis were produced by drugs which mimicked the action of parasympathetic sacral outflow and the central theme of their exposition is the thesis that "mucous colitis is a physiologic disorder of the colon brought about through the action of the sympathetic nervous system," and that the commonest cause of parasympathetic overstimulation in mucous colitis is emotional tension. This tension was obviously present in 92% of the psychogenic cases in their series. The prognosis for cure is bad because the major emotional problems are usually insoluble. The treatment of such patients consists largely in mental hygiene, including insight, assistance in solving conflicts, social adjustments, disciplinary management, reassurance and transference, suggestion and resolution of the neurosis possibly by a Freudian analysis. In addition, symptomatic therapy may be helpful.

(*b*) *Non-specific Ulcerative Colitis.* Testimony is accumulating that it is a psychosomatic disease. It is tempting to regard non-specific ulcerative colitis as an advanced phase of mucous colitis or spastic colon but thus far the testimony of experienced gastro-enterologists[9,12,53] does not permit this conclusion. In my comparatively limited experience, there is no such intermediate clinical phase; the transition from apparent health to the clinical evidence of disease is abrupt. Nevertheless, in a considerable number of patients one can unearth a history that in childhood under the influence of emotional distress, the bowels moved at least 2 or 3 times. Sullivan[49] and Cullinan[12] noted this occurrence in a number of their patients with ulcerative colitis and, in others, a history of spastic constipation. Despite the apparent species difference, in non-specific ulcerative colitis as in mucous colitis, all the normal functions of this gut are exaggerated, upon which are superimposed the exudative manifestations of the inflammatory process.

Murray[39] was the first to emphasize the rôle of psychogenic factors in non-specific ulcerative colitis. He reported 12 cases. After com-

menting that a state of emotion is often accompanied by hypermobility, spasticity, hypersecretion and vasomotor disturbances, he believes that these disturbances can be transmuted into a physical condition, if the emotional conflict is deep seated or chronic, if there is a specific organism, or if the individual is predisposed by heredity, early training, etc. He found beside fearfulness, emotional immaturity in their mental make-up. Of 7 men, 6 were tied to their mothers and 1 substituted an elder sister for his mother. None were married. Of the 5 women, 3 were married, 1 to a man of her own age. The most frequent conflict arose from the mother attachment and the desire to get married. It is not so much the sudden fright but a new situation which keeps the patient in a state of constant apprehension. Their characters may be described as analerotic with masochism and sadism.

Sullivan[49] reported the psychiatric data on 15 patients. Many of the patients were neat and fussy. Ten patients showed an inability to throw off the effects of an emotional episode. Financial worries occurred in 8 of the 15 and sexual maladjustment was present in all but 2 cases. Five of the males showed abnormal attachments to the mother; in the remaining 5 there was an attachment to some close relative. There is an amazingly close chronologic association between emotional episodes and the onset of the diarrhea. In 11, the bloody diarrhea began within 48 hours of the upset. In the other 4, the emotional state was a prolonged one, but in this group the exacerbation of the diarrhea was as closely dependent on the emotional state as in the first group. Psychotherapy produced striking results when other methods failed.

Wittkower[55] regards ulcerative colitis as a disease of the mentally ill or maladjusted. Almost all of his patients showed character disorders, obvious neurosis or psychosis. He divides his patients into 4 groups: (1) the obsessional—those characterized by overconscientiousness, overscrupulousness, cleanliness and abstinence; (2) the hysterical—those characterized by emotional lability, temper, tantrums, childishness, self-centeredness and suggestibility; (3) a less well-defined group containing some schizothymics and depressives; (4) miscellaneous personality types. In 37 of 40 patients, the colitis or its recurrence was antedated by disturbing events. He also justifies psychotherapy in the treatment of the disease.

Daniels[14] studied 25 cases in the Constitution Clinic at the Presbyterian Hospital. Of 14 cases that were studied intensively comprising 2 men and 12 women, 8 showed a pathologic attachment to a relative; in 6, the death of this relative had been of paramount importance. Indecision concerning marriage was marked in 2 unmarried members of this group and in 2 others engagement and marriage were the precipitating causes. In 2 cases, the onset of symptoms was associated with childbirth, which also played a prominent rôle in another. Money difficulties were significant in 4 cases. He submits a detailed report of 3 patients. Good results are reported by psychotherapy.

From the psychoanalytic viewpoint, Alexander[1] contrasts the colonic type of patient as dependent, anal receptive and oral aggressive, in

contrast to the gastric ulcer type, characterized by "an inner rejection of passive receptive and oral aggression tendencies." Alexander stresses the symbolic use of feces as an expression of hostility, and sometimes as the equivalent of childbirth, an observation noted by Daniels in one of his patients.

In a study of 100 or more cases of non-specific ulcerative colitis in the Mt. Sinai Hospital, I have been strongly impressed by the psychosomatic relationship. As others have noted, there was a close relationship between the onset or exacerbation of symptoms and an emotional upheaval. Indeed, a psychosomatic study is part of the history of every case of ulcerative colitis admitted to the Mt. Sinai Hospital. Often the onset of symptoms was not occasioned by a catastrophic insult but by a prolonged conflict attendant upon a life situation into which the patient found himself propelled. The three dominant life situations that affected these patients were, in the order of frequency, parental fixation, marriage and money, not by any means always sharply demarcated but with interrelationships. Sexual maladjustments were common, as indicated by the frequency in which the onset occurred during and immediately after a honeymoon. There were no apparent anthropologic constitutions, nor was there any particular age incidence, although the majority occurs in the 2d and 3d decades. According to the pediatrists children below the age of 10 are rarely affected.

Psychologically, I have found that they are usually soft and non-aggressive, fussy and overconscientious, sensitive and immature, weak-willed, narrow horizoned and, as White, Cobb and Jones found in mucous colitis, altogether utterly dependent individuals. Like others, I have found that occasionally psychotherapy produces dramatic remissions of the disease, more likely in the early than in the chronic and advanced cases.

The mechanism whereby psychogenic influences produce this serious disease is entirely speculative. It is permissible to state that hyperkinesis is a predominant part of the mechanism and that it is mediated through the pathways of the vegetative nervous system. Experimentally, lesions simulating non-specific ulcerative colitis have not as yet been reproduced. To my view, the most promising lead for the interpretation of the mechanism is that of Lium,[27] who made explants of the colon in the abdominal wall. He showed that these explants react to various stimuli by a spastic contraction of the musculature with discharge of mucus and with hemorrhage and ulceration. These stimuli include mechanical stimulation, parasympathomimetic drugs, such as acetylcholine and prostigmine and dysentery toxin. It is conceivable that overstimulation of the vegetative nervous system produced by psychologic influences may produce the same effect as parasympathomimetic drugs. In this connection, it is interesting that White, Cobb and Jones produced changes in the rectal mucosa stimulating those observed in mucous colitis by the oral administration of acetyl-beta-methylcholine.

Hyperkinesis is well illustrated in the genesis of the psychoses; but

these differ from the forementioned hyperkinetic diseases in that, although the sequence from the larval to the labile finally into the fixed stage can be readily traced, morbid anatomic changes, at least thus far, have not been demonstrated.

6. *Manic-depressive Psychosis.* The exaggeration of function that this malady represents may be called the normal rhythm of life, in which the swings between ecstasy and depression are low and to which the average person readily adjusts himself. If one has known a patient intimately before the onset of a manic-depressive psychosis, one can invariably recall that the patient always possessed an abnormal excursion in his emotional range. Indeed, the constitution of the manic-depressive is almost identical with that of Graves' syndrome. The emotions pass from ecstasy to depression in rapid sequence; in fact, the incidence of manic-depressive psychosis in Graves' syndrome is by no means uncommon.[5] The patient is high-strung, deeply emotional, narcissistic, violent in his expressions and anxious. He belongs to the type of individual whom I have described as "allergic to life." This type, as I tried to show, is to a large extent the result of environmental influences dating from the earliest years of life, in most instances, maternal overprotection. But there must be a genetic component as well, because all psychiatrists are agreed that manic-depressive psychosis is commonly hereditary.[5,8] As in so many of the hyperkinetic diseases, the pronounced attack of manic-depressive psychosis and its prolonged fixation dates from a sudden emotional strain or prolonged mental conflicts. When the psychosis comes, the individual is not different but an exaggeration and fixation of his former self.

7. *Paranoia.* Paranoia may be regarded as an exaggeration of the normal effective state of the mind. My limited experience with patients whom I have known well and who have developed paranoia has afforded the conviction that I have been observing nothing more than exaggeration and fixation of personality trends. These folk have always been suspicious, eccentric and afflicted with profound obsessions. This impression is confirmed by the observations of experienced psychiatrists. Thus White[52] quotes Mangan as saying, "They show peculiarities during childhood, manifesting themselves in a certain taciturnity, moroseness or disinclination to associate with other children as freely as usual. The child may also have shown a tendency to make friends with an older person, stay at home and read and sew instead of play and may have a tendency to day dreams and the building of air castles." This period may be termed, according to the psychiatrists, the hypochondriacal stage; this is followed by the stage of persecution and finally by the stage of transformation of the personality. Church and Peterson[10] say that paranoia "affects by preference individuals who are even in their childhood, peculiar, morbid, shy, irritable, mistrustful and misanthropic." "Puberty and adolescence tends to intensify the morbid peculiarities already present." Braude[8] comments that from childhood, the make-up of the paranoic is egocentric, selfish, suspicious, proud and mystic; he is impatient and defiant of conventions. Sadler[45] says that paranoia develops in

persons who are suspicious, sensitive, jealous, as well as those who suffer from an inordinate ambition. Paranoid trends are also more likely to develop in shy, dreamy, selfish, prudish and impractical individuals. Sadler and Adolph Meyer[31,45] even speak of a paranoid constitution. All are agreed that heredity is a strong predisposing factor in paranoia. The mechanism whereby this type personality is transformed into a psychosis is not pertinent to our thesis, nor, indeed, is there any agreement on the part of psychiatrists. But at all events, in this psychosis as in the hyperkinetic diseases that we have discussed the transition can be traced from a basic constitution, conditioned by heredity, to a labile and finally to an intensification and fixation of symptoms.

I am quite sure that I have not exhausted the list of hyperkinetic diseases. For instance, I am confident that the tone of the bronchial musculature plays a rôle in certain forms of asthma of psychogenic origin and that persistent bronchial spasm and compensating phenomena lead to emphysema and eventually to hypertension of the pulmonary circuit and its cardiac sequelæ. Also, I have reason to believe that some forms of schizophrenia subscribe to this pattern. My purpose rather has been to submit a concept. The major problems in the study of the hyperkinetic diseases are two: (1) The mechanism whereby the impact of environmental influences upon a constitutional background bring about disease. Inasmuch as the hyperkinetic diseases are essentially human diseases, experimental methods to reproduce them have largely failed because they cannot introduce the human equation. (2) The determination of the reason why one function is predominantly involved. The concept of "organ inferiority" is thus far entirely speculative. The answer probably lies, as Dunbar[18] puts it, "in the various combinations of heredity and constitutional factors, specific conflicts in the course of development, and the total personality organization, plus adventitious factors." White, Cobb and Jones say, "It is not the objective fact of impact which is important but the way in which it is experienced." We may call attention at this point to the fact that there is no specificity between psychosomatic factors and the hyperkinetic function, the proof lying in the not infrequent association in the same patient of two hyperkinetic diseases and indeed of all aspects of psychosomatic medicine. In the solution of these problems the general practitioner possesses a decided advantage over those engaged in exclusive hospital practice because the latter see only a small cross-section, usually the terminal, of the life cycle of the disease. This limitation applies as well to the psychiatrist, although the latter is indispensable in the elucidation and interpretation of the background and the mental workings of the patient. What is needed is a balanced combination of all. It is encouraging that intensive study of the psychosomatic diseases has already been begun in the Psychosomatic Clinic at the Presbyterian Hospital in New York City and the Psychanalytic Institute in Chicago.

The maladies I have described have certain common denominators:

A. These diseases have as backgrounds a constitution which is usually both genotypic and phenotypic. The direct stimulus is a maladjustment either sudden or protracted to the trials and tribulations of modern civilized existence. These two factors may be compared as the tinder and the spark, analogous to what occurs in infection.

B. There is an exaggeration of function. It is well established that emotion even in the apparently normal being can cause an elevated blood pressure, rise in the basal metabolic rate, an increase in secretion and in the acidity of the stomach, an increase in the tonus of the cardiac sphincter and an increase in the peristalsis and increased secretion of the colon, and it is plausible to assume that if these emotional reactions continue and are profound enough that they may cause a fixation of the hyperkinesis. In all likelihood, this mechanism is mediated through the vegetative nervous system.

Curiously, the only psychosomatic disease I am aware of in which normal functions are depressed is that strange malady known as *anorexia nervosa*. This malady in its severe forms may be regarded as the expression of a wish to die or spiritual suicide. Patients hesitate to take their lives but reduce every item of living to the lowest possible terms. Clinically, though not etiologically and pathologically, it resembles Simmonds' disease and is characterized by profound loss in weight, a subnormal body temperature, a lowered basal metabolic rate, diminished sexual activity, amenorrhea, slow pulse, a lowered blood pressure and hypochlorhydria. Indeed, there are so many features that resemble hibernation, in which the pituitary gland represents part of the mechanism, that one wonders whether the difference between Simmonds' disease and anorexia nervosa consists solely in the fact that in Simmonds' disease the primary change in the pituitary gland is organic and in anorexia functional. The disease appears to be exquisitely psychogenic in origin, most often the result of excessive parental domination. In fact, the disease responds well to psychotherapy. At all events, it is a mystery why in this disease of psychosomatic origin so many of the normal bodily functions should be depressed instead of being elevated.

C. These hyperkinetic diseases are essentially human diseases and more particularly of civilization. There is ample testimony that they are rare or uncommon in primitive people and when they do occur in such folk, it is only when they are in competition with the white race. With the exception of peptic ulcer and then only rarely, these diseases have not been observed spontaneously in the lower animals. Nor, indeed, can these methods be satisfactorily reproduced experimentally except by methods that are unphysiologic in the human race.

D. These hyperkinetic diseases rarely occur before the age of puberty when the emotive faculties become more subtle and adjustment to life becomes more sensitive and complex.

E. These hyperkinetic diseases have an unusual tendency to recur. This is not to be wondered at when one considers that the disease is so closely allied to the ego, and how difficult it is to eliminate completely

a normal function of the body. Of all the functions that I have listed the only one that can be eliminated is gastric acidity. If an achlorhydria can be produced by subtotal gastrectomy, one can be assured that the patient will not have a recurrence of his peptic ulcer. In subtotal thyroidectomy for Graves' syndrome, one only removes part of the total metabolism for the thyroid gland is only responsible for 40% (Means[30]). Recurrence after operation for Graves' disease is always possible, first, because the personality remains, and, second, because complete adjustment to the old environment has not taken place. Essentially, the treatment of the patient really begins when the operation has been completed.

F. Inasmuch as the transition from the normal or static phase to the abnormal is subtle and the line of demarcation is indefinite, there can be no specific diagnostic tests for these diseases, only an arbitrary one. All bodily functions have ranges within the normal, not a precise mathematical quantity. The diagnosis of these diseases therefore depends upon a perspective of the composite picture, in which a study of the personality of the patient and his life history is a vital consideration.

As a rule, the hyperkinetic diseases evolve through 5 discernible stages: (1) the constitutional; (2) the exaggeration of function; (3) the lability of signs and symptoms; (4) the fixation of this exaggerated function; (5) somatic changes. In other words, the time factor is important in the genesis of these diseases. Relativity has its place in medicine as it does in physics.

Summary. The concept is submitted that certain diseases that may be called "hyperkinetic" represent primary exaggerations of normal bodily functions with morbid anatomic changes as a sequel, instead of the usually accepted reversed order of disease process. Tentatively, the following diseases are submitted: (1) Hypertension of the greater circulation, which represents an exaggeration of the normal intra-arterial pressure and leads to arteriosclerosis and the cardiovascular-renal syndrome. (2) Graves' disease, which represents, in greater part at least, an exaggeration of the normal basal metabolic rate. (3) Peptic ulcer, in which one of the dominant expressions is the exaggerated acidity and secretion of the normal stomach. (4) Cardiospasm, which represents an increase in the normal tone of the cardiac sphincter. (5) "Spastic colon," mucous "colitis" and ulcerative colitis, which represent exaggeration of the normal tonicity, peristalsis and secretion of mucus of the colon. (6) Manic-depressive psychosis, which represents an exaggeration of a normal rhythm. (7) Paranoia, which represents an exaggeration of the affective functions.

The biology of these diseases is discussed and possible mechanisms and new approaches are suggested. These maladies have certain common denominators. They possess a constitution that is usually a combination of phenotypic and genetic characters. The direct stimuli are maladjustments between the psyche and the environment. These diseases are essentially limited to the human species and are mostly products of civilization. Experimentally, they cannot be reproduced

in animals except by methods that are unphysiologic for human beings. They rarely occur before the emotive faculties are fully developed. They possess a remarkable tendency to recur. Because the transition from the normal to the abnormal is gradual, no specific diagnostic test is applicable, unless it is an arbitrary one. The diagnosis therefore must depend upon a study of the composite picture—the organ—personality. These diseases, as a rule, evolve through 5 stages: (1) constitution; (2) exaggeration of function; (3) a lability of signs and symptoms; (4) fixation of this exaggeration of function; (5) somatic changes.

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THE USE OF SULFAPYRAZINE IN INFANTS AND CHILDREN

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Studies of the absorption, excretion, and distribution of sulfapyrazine (2-sulfanilamidopyrazine) in adults have been reported by Hamburger, Ruegsegger, Brookens, and Eakin.[5] Comparison of studies on adults and on children receiving other sulfonamide drugs indicates that in the two groups the same relationship does not exist between the quantities of drug given and the concentrations obtained in the body fluids. For this reason, we undertook a study of the absorption and distribution of sulfapyrazine* in a group of infants and children with various infections, at the same time that we were attempting to determine the therapeutic value and the toxic effects of this drug.

Plan of Study. *Oral Administration.* Unselected hospitalized patients with various types of mild or moderately severe infections were given sulfapyrazine orally with as close adherence as possible to the following dosage scheme: 0.1 gm. per kilogram body weight was given as an initial dose, followed by 0.2 gm. per kilogram per 24 hours in 4 divided doses. Blood levels† of the free drug were determined at intervals during the course of several days of drug administration.

* We are indebted to Mead Johnson & Co., Evansville, Ind., through Dr. Warren M. Cox, Jr., of the Research Laboratory for the generous supply of sulfapyrazine and sodium sulfapyrazine used in this study.

† The sulfapyrazine determinations were carried out by the method of Bratton and Marshall[3] adapted to determination on 0.1 cc. of fluid. Because many of the patients were small infants, most of the blood samples were obtained by skin puncture. Therefore, in order to have comparable values, the determinations were made on whole blood except in certain isolated cases, although the level of drug in the plasma affords a better approximation of the level in the intercellular fluid.[7]

Subcutaneous Administration of Sodium Sulfapyrazine. Selected hospitalized patients with more severe infections were given sodium sulfapyrazine subcutaneously as a 0.5 or 1.0% solution in Ringer's or lactate-Ringer's solution. The dosage was varied as indicated in the charts, and frequent determinations of the levels of free sulfapyrazine in the blood and in some cases in the spinal fluid were made.

Therapeutic and Toxic Effects of Sulfapyrazine Administration. Careful observations of the clinical course and toxic effects were made on 236 cases with various types of infections treated at St. Louis Children's Hospital and 22 cases with meningococcus meningitis treated at the Isolation Hospital of St. Louis.

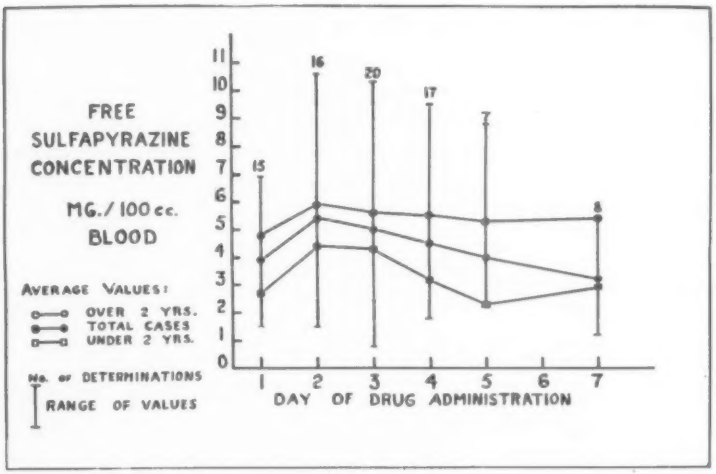

CHART 1.—Blood levels of free sulfapyrazine in patients receiving orally an initial dose of 0.1 gm. per kg. followed by 0.2 gm. per kg. per 24 hours in 4 divided doses.

Results. *Absorption of Sulfapyrazine Following Oral Administration.* Chart 1 shows the range and average blood levels of sulfapyrazine on successive days in a group of patients receiving the drug by mouth as indicated. The averages for the entire group and for those patients over and those under 2 years of age are shown separately. The average of all of the determinations for the entire group was 4.3 mg. per 100 cc.; for those over 2 years of age 5.3 mg. per 100 cc.; and for those under 2 years of age 3.3 mg. per 100 cc. Lower blood levels in infants on proportionate dosages have been noted with the other sulfonamide drugs.

In Chart 2 is shown the change in the free sulfapyrazine blood levels between the 4th and 6th hours after the oral administration of the drug in patients receiving the drug at 6 hour intervals. This change represents an average fall of only 11% which is similar to that observed with sulfapyridine and sulfadiazine and much less than that seen with sulfanilamide and sulfathiazole.

Blood Levels Following Subcutaneous Sodium Sulfapyrazine. Chart 3 shows the blood levels of free sulfapyrazine observed over periods of from 5 to 12 hours in 5 patients who had each received a single subcutaneous injection of 10 cc. of a 1% solution of sodium sulfapyrazine per kilogram body weight. Comparatively high blood levels were reached quite rapidly following the subcutaneous injection. Chart 4 shows the *plasma* levels of free sulfapyrazine obtained on one patient who received the above dose on several different days. Wide variations in the rate of urine flow on these different days were accomplished by forcing or restricting water by mouth preceding and during the experiments.* Charts 5 and 6 show the blood levels of free sulfapyrazine obtained in different patients receiving repeated doses of sodium sulfapyrazine subcutaneously in the amounts indicated. It may be

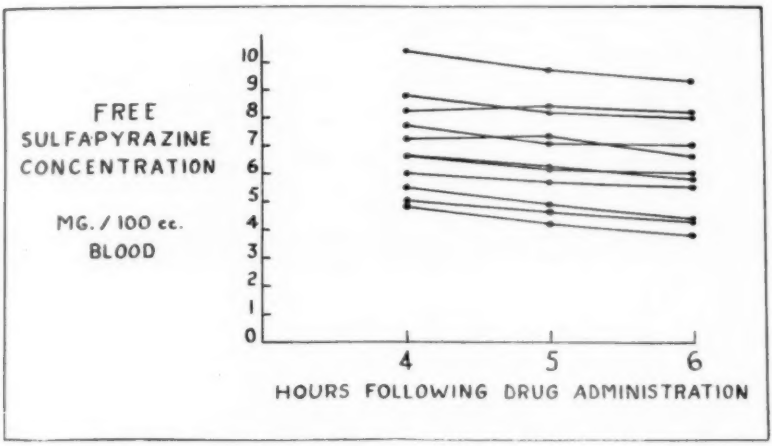

CHART 2.—Change in free sulfapyrazine levels between 4th and 6th hour in patients receiving drug orally in dosages approximately equivalent to 0.2 gm. per kg. per 24 hours at 6 hour intervals.

seen that after a high initial blood level of the drug has been attained by the subcutaneous administration of 40 cc. of 0.5% solution of sodium sulfapyrazine per kilogram body weight (see below), high concentrations can be maintained by repeated subcutaneous injections of 20 cc. of 0.5% solution of the drug per kilogram every 8 to 12 hours. In some cases, however, there may be mounting drug concentrations in the blood, and in others there may be some falling off of the levels when the injections are repeated at these intervals. In severely ill patients, it is desirable to obtain a high initial level of the drug in the body fluids as quickly as possible. Chart 7 shows the rapidity with which this can be accomplished when 40 cc. of 0.5% solution of sodium sulfapyrazine per kilogram body weight is given. Chart 8 shows the very

* From the plasma clearances determined on this patient,[2] it appears that these variations in plasma levels of sulfapyrazine following the subcutaneous administration of the sodium salt may be more directly related to variations in clearance than to variations in urine flow.

rapid rise in the blood concentration to levels of 30 to 40 mg. per 100 cc. within a few hours when 80 cc. of 0.5% solution is given in one injection or when 40 cc. is given and repeated after 2 to 5 hours. We

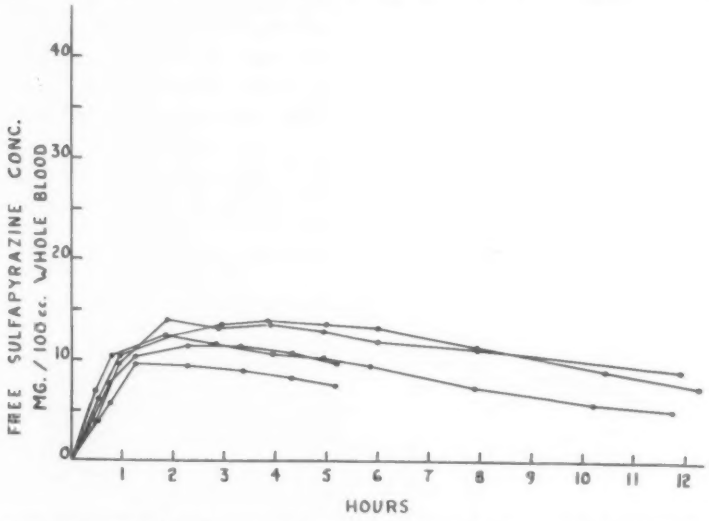

CHART 3.—Whole blood levels of free sulfapyrazine in different patients following single subcutaneous injections of 10 cc. of 1% solution of sodium sulfapyrazine per kg.

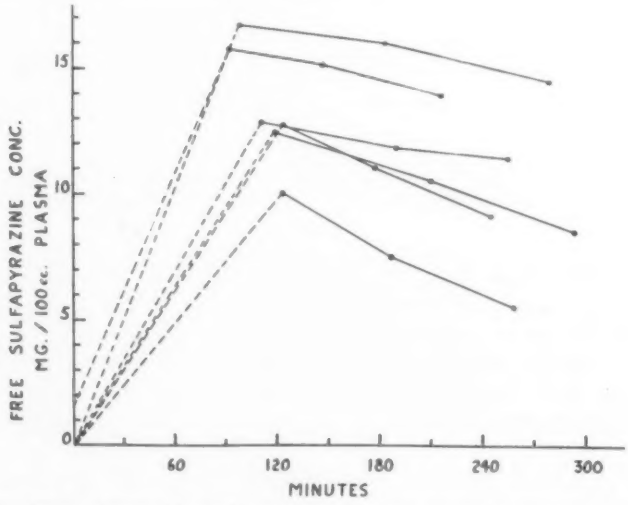

CHART 4.—Plasma levels of free sulfapyrazine in a single patient receiving subcutaneously 10 cc. of a 1% solution of sodium sulfapyrazine per kg. on each of several days.

believe that the subcutaneous administration of the sodium salt of sulfapyrazine offers several very definite advantages over the intravenous route of administration, particularly in infants and children. (See Discussion.)

Sulfapyrazine in Cerebrospinal Fluid. Table 1 shows the relationship between plasma and spinal fluid concentrations of sulfapyrazine in patients with meningitis who were receiving repeated subcutaneous

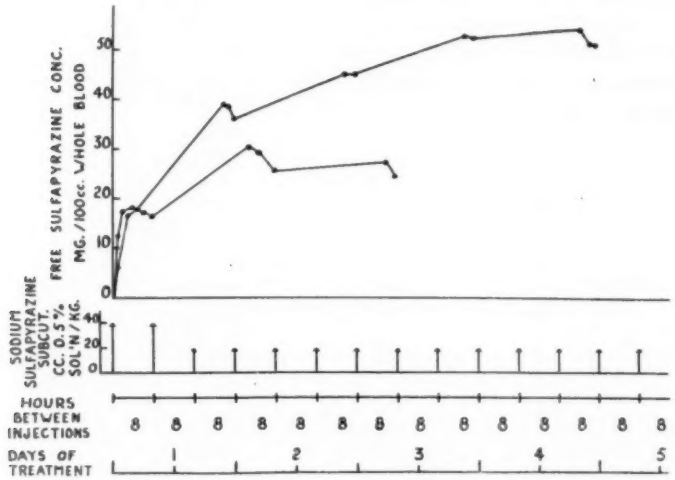

CHART 5.—Whole blood levels of free sulfapyrazine in 2 patients receiving subcutaneously repeated doses of 20 cc. of 0.5% solution of sodium sulfapyrazine per kg. every 8 hours after a high initial level had been established.

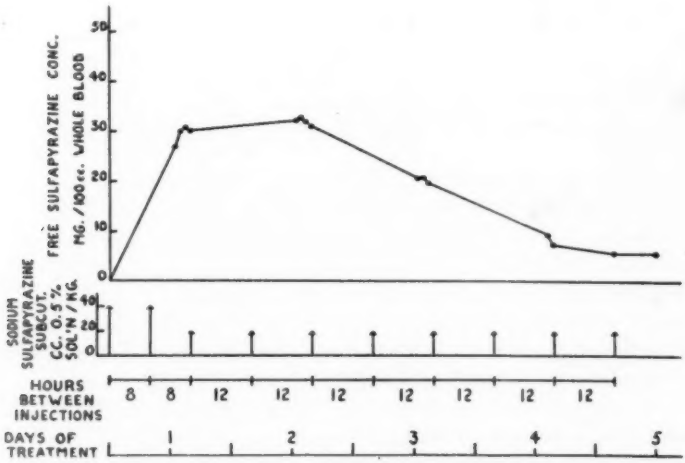

CHART 6.—Whole blood levels of free sulfapyrazine in 1 patient receiving subcutaneously repeated doses of 20 cc. of 0.5% solution of sodium sulfapyrazine per kg. every 12 hours after a high initial level had been established.

injections of sodium sulfapyrazine as shown in Charts 5 and 6. Whole blood determinations were made at hourly intervals for periods of from 2 to 6 hours preceding the simultaneous sampling of plasma and spinal fluid, and during these periods the levels showed a maximum variation

of only 13.8%. We feel that a knowledge of the constancy of the blood levels preceding the simultaneous drawing of different body fluids for the purpose of studying distribution of substances is very important.[1] The per cent of the *plasma* concentration occurring in the spinal fluid varied from 50.8 to 81.8% with an average of 64.4% (76.2% of the whole blood level), which is somewhat higher than that observed by Hamburger and his associates,[5] who found 50 to 60% of the *whole blood* concentration in the spinal fluid 12 hours after the intravenous injection of sodium sulfapyrazine.

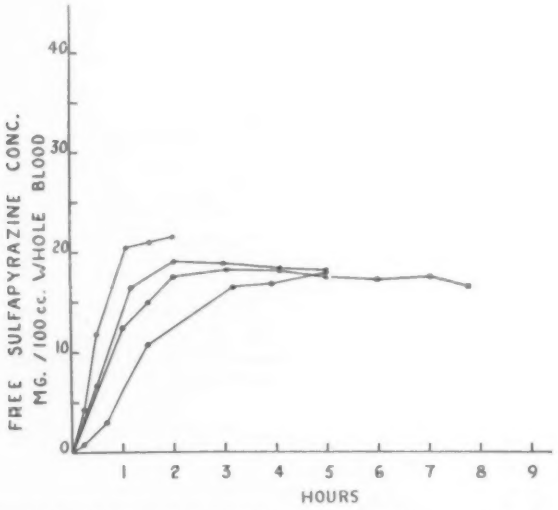

CHART 7.—Whole blood levels of free sulfapyrazine in different patients following single subcutaneous injections of 40 cc. of 0.5% solution of sodium sulfapyrazine per kg.

Evaluation of Therapeutic Effectiveness of Sulfapyrazine. In a period of 8 months between September 13, 1942 and May 14, 1943, 258 infants and children were treated with sulfapyrazine. No selection of cases was made, and the types of infections treated represented the wide variety commonly seen in a children's hospital. No single type of infection occurred frequently enough to allow a statistical comparison of the effectiveness of sulfapyrazine with that of other sulfonamide drugs previously studied.[6] However, patients with certain specific types of infections have served in the past as a basis for the evaluation of the effectiveness of other sulfonamide drugs,[6] and the results with sulfapyrazine in the treatment of these patients are reviewed.

Lobar Pneumonia. Only 18 cases of lobar pneumonia were treated. There were no deaths, and all showed the type of prompt improvement that has been observed with the use of sulfapyridine, sulfathiazole, and sulfadiazine.

Meningococcus Meningitis. Twenty-seven cases of meningococcus meningitis were treated. All of the patients recovered. Twenty-two of them were included in a larger series of cases of meningococcus

meningitis, to be reported by one of us (D.G.), in which approximately 200 patients in one epidemic were treated with either sulfapyridine, sulfadiazine, sulfathiazole, sulfamerazine, or sulfapyrazine. In this series no difference in the therapeutic effectiveness of the various drugs could be determined by clinical or laboratory means.

Erysipelas. Three cases of erysipelas or erysipeloid infection were treated with sulfapyrazine with the very prompt response expected from the use of other sulfonamide drugs.

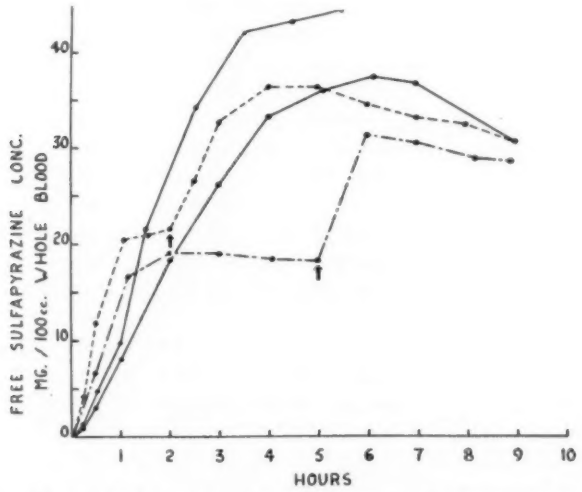

CHART 8.—Whole blood levels of free sulfapyrazine in different subjects following single subcutaneous injections of 80 cc. of 0.5% solution of sodium sulfapyrazine per kg. (———); and of 40 cc. per kg. repeated 2 hours (– – – –) and 5 hours (— — —) after first injection. Arrows indicate time of second injection.

Staphylococcus Infections. Eight cases of severe staphylococcus infection including 1 case of pneumonia; 5 cases of empyema, 1 with septicemia; and 2 cases of osteomyelitis with septicemia were treated with sulfapyrazine. The cases with septicemia received penicillin therapy also, and it was not possible in these or in the other cases to determine how much effect sulfapyrazine may have had on the course of the infection. It is thought, however, that there was no greater effect with sulfapyrazine than with other sulfonamide drugs.

Influenzal Meningitis. Five cases of influenzal meningitis were treated with sulfapyrazine. High concentrations of the drug in the blood and spinal fluid did not appreciably affect the course of the disease. All of these patients died. However, none of them was treated early in the course of the infection, and 4 of them were under 1 year of age. The 5th, a 2-year old child, had a chronic form of the disease.

Tuberculous Meningitis. Three cases of tuberculous meningitis were treated with very large amounts of the drug with no observable effect.

Bacillary Dysentery. Four cases of bacillary dysentery were treated. The response was good in each case.

Pyelitis. Four cases of pyelitis, in 3 of which the colon bacillus was recovered and in 1 of which no organism was found, were treated, and the improvement was very prompt.

Miscellaneous Infections. These included a large number of cases of non-specific upper and lower respiratory infections and several cases in which the drug was used prophylactically. An evaluation of the effectiveness of the drug in these patients is not possible.

Clinical Toxicity of Sulfapyrazine. Careful clinical observations and laboratory examinations relating to certain of the common toxic effects of other sulfonamide drugs were made on all the patients receiving sulfapyrazine.

Nausea and Vomiting. Nausea and vomiting clearly attributable only to sulfapyrazine did not occur in any case. This side-effect of the sulfonamide drugs occurs less frequently in infants and children than in adults, and in the former it is more difficult to determine whether the symptoms are due to the drug or to the infection for which the drug is being given. It seems clear, however, that sulfapyrazine causes as little or possibly less nausea and vomiting than the sulfonamide drugs commonly used at present.

Fever. Presumptive drug fever occurred in 5 cases. This number represents an incidence of only 1.9%.

Rash. No cases of cutaneous reactions due to sulfapyrazine were encountered. We do not feel that the failure to observe cutaneous reactions associated with sulfapyrazine administration to this number of patients indicates that such reactions will not occur. In our experience, however, it would be unusual with the other sulfonamide drugs, and particularly with sulfathiazole, for this number of cases to have been treated without the occurrence of drug rash.

Leukopenia. In no case was a leukopenia found which was thought to be due to sulfapyrazine. An analysis of the duration of drug treatment in all of the patients was not made, but many patients received the drug over a period of from 10 days to 2 weeks.

Acute Hemolytic Anemia. No cases of acute hemolytic anemia occurred in this series.

Renal Complications. Because of both their frequency and their seriousness, it is our feeling that the renal complications produced by the sulfonamide drugs, exclusive of sulfanilamide, constitute the most important of their toxic effects. Although there does not appear to be a strict correlation between blood levels of the drug or urinary output on the one hand and the occurrence of renal complications on the other,[1] the two factors mentioned do appear to bear some relation to the formation of renal calculi.[4] The lack of correlation, however, has suggested that other and unknown factors may be involved. For these reasons it is difficult to compare the incidence of renal complications from the various drugs as reported by different observers, and it is important that the height of the blood levels, particularly, be considered in relation to the occurrence of renal complications. In addition, it is

of greatest importance that the term renal complication be defined since some authors have limited it to the occurrence of pain over the kidneys, gross hematuria, and anuria or definite oliguria.[4]

In an analysis of the maximum blood levels of free sulfapyrazine observed, the cases were separated into two groups. The first includes 218 cases in which the blood levels of the free drug were less than 15 mg. per 100 cc. The second includes 40 cases in which the blood levels ranged from 15.3 to 59.4 mg. per 100 cc. (average 32.9 mg. per 100 cc.).

On the basis of clinical and laboratory findings, we have considered the cases of renal complications occurring in this series to be of two types. The first includes cases with only *transitory*, microscopic hematuria without any associated symptoms. These would have undoubtedly been overlooked had not careful, repeated examinations of the urine been made. This type occurred in 17 of the 218 cases in the first group, representing an incidence of 7.8%. There were 7 such cases in the second group of 40 patients, representing an incidence of 17.5%. In some of these cases it was difficult to be certain that there were more red cells in the urine than are commonly seen in the urine of severely ill infants and children not receiving a sulfonamide drug. The administration of sulfapyrazine was not discontinued because of this hematuria, and it subsided within a period of 1 to 3 days.

The second type of renal complication was that in which gross hematuria occurred. There were only 2 cases of this type in the entire series, representing an incidence of 0.78%. One of these cases occurred in each of the two groups described, representing an incidence of 0.46% in the group with lower blood levels and an incidence of 2.5% in the group with higher blood levels. In the former case there was no nitrogen retention or oliguria and the hematuria subsided in 1 day. In the latter case there was nitrogen retention and oliguria, both of which together with the hematuria gradually subsided over a period of 6 days after the drug was stopped.

It seems worth emphasizing that only one case of gross hematuria occurred in a group of 40 patients whose maximum blood levels of sulfapyrazine ranged from 15.3 to 59.4 mg. per 100 cc. (average level 32.9 mg. per 100 cc.*).

Other Toxic Effects. None of the other toxic effects which have been reported as due to other sulfonamide drugs was encountered in this series of cases treated with sulfapyrazine.

Discussion. Blood levels of free sulfapyrazine during oral administration of the drug in the dosages used are definitely lower than those obtained with equivalent dosages of sulfadiazine and possibly somewhat lower than those obtained with sulfathiazole. These lower blood levels occur particularly in patients under 2 years of age. They do not appear to be due to any greater difficulty in administering the drug

* We did not make a special study of the effect of maintaining an alkaline urine on the incidence of renal complications. In the majority of the cases treated with sodium sulfapyrazine subcutaneously a lactate Ringer's solution was used in making the 0.5% solution of the drug.

by mouth. Low blood levels after oral administration of sulfapyrazine were also found by Hamburger *et al.*[5] in adult human subjects and by Schmidt and Sesler[8] in mice. These lower levels might seem to be a disadvantage in the treatment of infections in infants and children by the oral administration of sulfapyrazine, although Schmidt, Ruegsegger, Sesler, and Hamburger[9] have found in mice that the milligram for milligram antipneumococcal activity of sulfapyrazine is greater than that of sulfadiazine. Concentrations of free sulfapyrazine in the blood change so little from the 4th to 6th hour after the oral administration of the drug that quite uniform levels can be maintained by giving the drug at 6-hour intervals. Schmidt and Sesler believe that the superiority of sulfapyrazine over sulfanilamide, sulfapyridine, and sulfathiazole in the treatment of beta hemolytic streptococcus infections in mice is due largely to the maintenance of effective concentrations in the blood during the entire period between administrations. In mice they found also that increasing the oral dosage of sulfapyrazine produced smaller increases in the concentration in the blood than were produced by the other sulfonamide drugs. Although we did not investigate this point specifically, the low blood levels observed in a few patients receiving very large dosages of sulfapyrazine by mouth suggest that it is also true for human patients. Schmidt and Sesler attribute this finding to the slow absorption of the drug from the gastrointestinal tract. The fact that high blood levels are maintained with comparable amounts of the drug given parenterally (see below) indicates that the low levels after oral administration are not due to rapid excretion.

TABLE 1.—RELATIONSHIP BETWEEN WHOLE BLOOD, PLASMA AND SPINAL FLUID CONCENTRATIONS OF FREE SULFAPYRAZINE IN 3 PATIENTS WITH MENINGITIS TREATED WITH SODIUM SULFAPYRAZINE SUBCUTANEOUSLY

Case	Day of drug administration	Variation in whole blood levels of sulfapyrazine preceding plasma and spinal fluid sampling		Free sulfapyrazine concentration mg./100 cc.			Whole blood concentration of sulfapyrazine present in spinal fluid (%)	Plasma concentration of sulfapyrazine present in spinal fluid (%)
		%	Hours	Whole blood	Plasma	Spinal fluid		
M. A.	1	11.0	6	16.4	20.7	10.5	64.0	50.8
	2	5.7	7	25.7	32.5	22.9	89.1	70.6
	3	11.2	2	24.6	28.6	23.4	95.1	81.8
J. P.	2	3.7	3	36.2	44.1	29.5	81.5	67.0
	4	0.7	3	53.0	58.9	40.6	76.6	69.0
	5	2.9	3	52.1	59.5	39.2	75.2	65.8
S. S.	2	13.8	3	30.2	36.0	18.6	61.9	51.7
	3	5.6	3	31.2	35.2	20.6	66.0	58.6
					Average		76.2	64.4

When high concentrations of the drug in the blood are desired, they can readily be attained by the parenteral administration of the sodium salt. We have limited our investigations to the subcutaneous administration of sodium sulfapyrazine because we feel that, at least in infants and children, its advantages are great enough to warrant its entirely replacing intravenous administration. By giving a 0.5% solution of

the sodium salt subcutaneously, the difficulties of intravenous administration in small infants are avoided. Very high blood levels can be attained within a period of 1 to 3 hours after beginning the administration, and at the same time the volume of fluid in which the drug is dissolved assures a good fluid intake. If very high levels are to be attained by intravenous administration to a patient with severe dehydration, lost fluids should first be replaced. With subcutaneous injection, however, this replacement of fluid is accomplished as the drug is being given, and consequently high blood levels may be attained just as rapidly. A final advantage of the subcutaneous over the intravenous route of administration is that the high blood concentrations are reached by a rapid rise *to* that level avoiding the excessively high levels which follow immediately after intravenous injections and during which the dangers of renal complications may be increased.

The percent of the plasma concentration of sulfapyrazine occurring in the spinal fluid (64%) is similar to that observed with sulfapyridine and sulfadiazine.

Our data do not allow any statistical comparison between sulfapyrazine and the other sulfonamide drugs as to effectiveness against the various infections in infants and children. However, a sufficient number of patients were treated and studied to warrant the opinion that with the dosages of sulfapyrazine and sodium sulfapyrazine employed, the effectiveness equals that of the other sulfonamide drugs.

It has been our feeling that a sulfonamide drug as effective as the ones now commonly used but one which produces fewer renal complications would be most desirable. It appears from our series that sulfapyrazine produces fewer severe renal complications than the sulfonamide drugs now commonly used with the exception of sulfanilamide. This seems particularly to be true in cases in which high blood levels of the drugs are maintained over a period of days.

Other toxic effects attributable to the sulfonamide drugs occurred no more and possibly less frequently in this series of patients treated with sulfapyrazine than would have been expected in series similarly treated with any other of the sulfonamide drugs.

Summary. From a study of the use of sulfapyrazine and sodium sulfapyrazine in the treatment of infections in a group of 258 infants and children, it was found that:

1. Comparatively low blood levels of free sulfapyrazine follow the oral administration of the usual amounts of the drug.

2. Comparatively uniform blood levels are maintained when the drug is given by mouth at 6-hour intervals.

3. High blood levels of the drug can be rapidly attained and maintained by the subcutaneous administration of sodium sulfapyrazine.

4. An average of 64.4% of the amount of sulfapyrazine in the plasma (76.2% of that in the whole blood) was found in the spinal fluid.

5. With comparable blood levels, the therapeutic effectiveness of sulfapyrazine appears to be equal to that of any of the commonly used sulfonamide drugs.

6. Sulfapyrazine appears to cause few toxic effects, and the renal complications appear to occur less frequently with the use of this drug than with other sulfonamide drugs except sulfanilamide.

We wish to thank Dr. Alexis F. Hartmann, who supervised the care of the patients, for his helpful suggestions throughout this study.

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STUDIES ON THE PENETRATION OF SULFONAMIDES INTO THE SKIN

II. Sulfathiazole, Sulfadiazine and Sodium Sulfacetimide*

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In the first report of this series,[11] a method was described for studying the rate and degree of absorption of sulfonamides into the intact skin of guinea pigs and humans from various ointment bases. Whereas most workers estimate topical absorption by blood levels, this paper described sulfonamide analyses of skin biopsies. The time of application of the ointment, and the concentration of sulfanilamide in the various ointment bases were varied.

It was concluded that there was no correlation between the degree of penetration of sulfanilamide and the type of ointment base, at least in regard to whether the base is of the water-in-oil or the oil-in-water type. Concentration of sulfanilamide has little effect on tissue levels reached, but time of application had some effect.

In the present report, 3 additional commonly used sulfonamides have been studied, with the same objectives, namely to determine the effect of concentration, time of application, and type of ointment base. In addition, a few studies are included in which, instead of intact skin,

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absorption by injured skin is described. Moreover, studies were made on absorption from wet-packs of sulfonamide solutions, the effects of detergents and solubilizers, and finally the relative retention of sulfonamides by the skin after topical application.

Methods. The methods of applying the sulfonamides to the skin of guinea pigs held in confining cages, and the method of analysis of skin biopsies after different application times, was described in detail in the first paper of this series.[11] It is necessary only to repeat here that the excess sulfanilamide and ointment were washed off the skin with soap and warm water, followed by shaving and rinsing with warm water; that the biopsies weighed approximately 100 mg.; and that the biopsies were hydrolyzed in hot HCl prior to coupling, diazotizing, and determining total sulfonamides in the filtrates by a photoelectric method.

The same 7 different ointment bases that were studied in the first report[11] were used, 2 oil-in-water emulsion type bases (O/W), and 5 water-in-oil (W/O). The emulsion types were determined microscopically on samples stained with Sudan III, and by the conductimetric method.* The compositions were as follows:

OINTMENT BASES

Oil-in-water	%
1. †Sodium lauryl sulfate	1
Stearyl alcohol	11
Cetyl alcohol	3
Spermaceti	11
Glycerin	11
Water	63
2. ‡Liquid petrolatum	41
Peanut oil	2
Triethanolamine	1
Stearic acid	3
Cetyl alcohol	2
Water	51

Water-in-oil	%
1. Petrolatum	60
Stearyl alcohol	20
Water	20
2. §A base consisting of oleic acid, white petrolatum and oleic acid esters and amides of diethanolamine	
3. Petrolatum	50
Lanolin (anhyd.)	50
4. ×A base consisting of alcohols, and cholesterol esters in petrolatum	
5. Cod-liver oil	20
Lanolin (anhyd.)	20
Petrolatum	55
Paraffin	5

The sulfonamides were incorporated in these bases at concentrations of 1, 5, 10 and 20%, by tile and spatula.

* Base 1 was classified by error as O/W base C in the first paper.[11]
† Modified from Pillsbury *et al.*[8]
‡ Modified from Hawking.[4]
§ Hydrosorb (Abbott).
× "Aquaphor" (Duke).

Experimental. 1. *Sulfathiazole Ointments.* Five and 10% concentrations of sulfathiazole in the 7 bases, and 1, 5, and 10% concentrations in Base 2, were compared, with application times of 1 and 3 days (2 applications daily). The results are summarized in Table 1, including a few human cases. The data is given as mg. per 100 cc. total sulfonamide concentration per 100 gm. wet weight of skin. Each figure represents averages of at least triplicate determinations from 1 piece of skin, that is 3 skin aliquots per biopsy. Each experiment was repeated at least 4 times. In many cases more than 3 aliquots were taken from each piece of skin.

TABLE 1.—PENETRATION OF SULFATHIAZOLE (SAT) INTO THE INTACT SKIN OF GUINEA PIGS AND HUMANS FROM VARIOUS OINTMENTS

Type of emulsion	Ointment base	1% SAT ointment. Av. mg. SAT per 100 gm. skin, after		5% SAT ointment. Av. mg. SAT per 100 gm. skin, after		10% SAT ointment Av. mg. SAT per 100 gm. skin, after	
		1 day	3 days	1 day	3 days	1 day	3 days
W/O	1	..	..	2.8	3.6	3.1	3.8
	2	5.6	7.5	4.6	6.4	4.1	7.9
	*5.1**	*7.3*		*6.6*	*7.8*	*5.6*	*5.8*
	3	..	..	2.5	3.2	2.8	4.2
	4	..	..	4.3	4.3	2.7	4.7
	5	..	..	2.5	3.2	2.7	3.7
O/W	A	..	..	3.0	3.2	3.1	3.8
	B	..	..	4.7	6.8	4.0	5.3

* Italics are human analyses.

It is seen that concentration of sulfathiazole has no effect on skin absorption, and that the time of application has a slight effect. The frequency of application may have an effect, but since 1 to 2 applications were made daily, this is doubtful. It is also seen that the type of ointment base used has little or no effect, at least with respect to the type of emulsion, whether of the oil-in-water, or the water-in-oil.

2. *Sulfadiazine Ointments.* Since there was no appreciable concentration effect, but a slight time effect with sulfanilamide[11] and sulfathiazole, it was decided to study the time and concentration effect of sulfadiazine at 1 and 10% concentrations only in one base. In this case, Base 2 was selected since it has been studied more extensively than the other bases, and comparisons could thus be made with the other sulfonamides. To determine the effect of the various bases, 1% sulfadiazine in the 7 bases was studied, and the biopsy concentrations were determined after 3 days application time. Table 2 shows the results.

Concentration has little effect except at 1 day application time, and time had a small but definite effect. Base 2 gave the best penetration, but there was no effect of the type of emulsion base, as in the case of sulfanilamide and sulfathiazole.

3. *Sodium Sulfacetimide.*† This salt was included in this study because of its high solubility and relatively low pH in comparison to the sodium salts of sulfathiazole, sulfadiazine, and sulfapyridine. The solubility of sodium sulfacetimide in water at room temperature

† We wish to thank Dr. Edward Henderson of the Medical Research Division, Schering Corp., for this material.

is 56.9%, with a pH of 9.5. At a 20% concentration in plasma, the pH is 7.68.[9] The sodium salts of the other sulfonamides, because of their high alkalinity, have been avoided in topical application, although Fox[1] claimed that sodium sulfadiazine is tolerated in fairly high concentrations, in contrast to sodium sulfathiazole.

TABLE 2.—PENETRATION OF SULFADIAZINE (SAD) INTO THE INTACT SKIN OF GUINEA PIGS FROM VARIOUS OINTMENTS

Type of emulsion	Ointment base	1% SAD ointment. Av. mg. SAD per 100 gm. skin, after		10% SAD ointment. Av. mg. SAD per 100 gm. skin, after	
		1 day	3 days	1 day	3 days
W/O	1	..	3.1		
	2	3.6	6.3	5.1	6.6
	3	..	2.9		
	4	..	3.6		
	5	..	3.9		
O/W	A	..	3.0		
	B	..	3.6		

In this study, 1, 10 and 20% sodium sulfacetimide in Base 2 were compared. The salt was first dissolved in a minimal volume of water and the resulting solution was emulsified with the melted base, using an egg beater. The effect of the various bases was studied, using only a 1% concentration, as in the case of sulfadiazine.

Table 3 shows the results.

TABLE 3.—PENETRATION OF SODIUM SULFACETIMIDE (NaSAC) ("ALBUCID SOLUBLE") INTO THE INTACT SKIN OF GUINEA PIGS AND HUMANS FROM VARIOUS OINTMENTS

Type of emulsion	Ointment base	1% NaSAC ointment. Av. mg. NaSAC per 100 gm. skin, after		10% NaSAC ointment. Av. mg. NaSAC per 100 gm. skin, after		20% NaSAC ointment. Av. mg. NaSAC per 100 gm. skin, after	
		1 day	3 days	1 day	3 days	1 day	3 days
W/O	1	3.3	7.3				
	2	5.5±1.6	12.4±3.6	6.0±2.2	14.2±3.6	5.1±1.8	21.3±2.8
		*5.8**	*14.7*	*6.9*	*19.2*		
	3	2.2	6.0				
	4	3.0	4.2				
	5	2.0	4.6				
O/W	A	3.5	4.6				
	B	5.2	5.0				

* Italics are human analyses.

Concentration has some effect, and time had a marked effect. The levels reached were higher than those with the less soluble sulfonamides already described. Base 2 gave a higher absorption than the other bases, but the emulsion type base had no effect, as with the other sulfonamides studied.

The sodium salts of sulfathiazole, sulfadiazine, and sulfapyridine caused saponification of some of the bases, and skin maceration, and were not studied.

4. *Solubilizers and Detergents.* It seemed plausible since sulfanilamide, sulfathiazole and sulfadiazine are little soluble in water, that the use of better solvents such as propylene glycol[14] and detergents and

solubilizers such as aerosol, to ointment bases, might increase the absorption of the sulfonamides.

Studies were therefore carried out with 1 and 10% sulfathiazole in a base consisting of propylene glycol 10%, aerosol (OT–70) 0.5%, Base 2 q.s. 100%. The sulfathiazole was suspended in the warm glycol, aerosol mixture, and then emulsified with the melted base with a beater. Skin concentrations after 1 and 3 days application time were almost identical with those obtained with the corresponding concentrations of sulfathiazole in Base 2 without the glycol and aerosol. It is difficult to incorporate higher concentrations of propylene glycol into ointment bases, as separation occurs, and although this probably could or has been done, higher concentrations probably would not cause higher penetration in intact skin. Injured skin might be entirely different, but we have not studied this problem. Herrmann *et al.*[6] developed new vehicles containing aerosol, xylene, antipyrene, and propylene glycol, which may have definite advantages as bases for sulfonamides. These workers also mention that they have developed histochemical methods for investigating sulfonamide penetration into skin. Such an approach would be of great interest if they could reveal the pathways of absorption.

5. *Studies on Injured Skin.* The hair on the left side of anesthetized guinea pigs was closely clipped and the skin injured with coarse sandpaper, rubbing until bleeding occurred. The uninjured skin on the right side of the same animal served as a control.

The studies were carried out with 1 and 10% concentrations of sulfanilamide and sodium sulfacetimide in Base 2. Tissue biopsies and analyses were made after 2 and 6 hours application time. The ointment was reapplied several times during this period.

In order to compare the penetration from an ointment with that from wet packs as two different methods of topical applications, a few data are included to illustrate this, although the present report does not purport to examine in detail the absorption from wet packs and solid powder. The penetration from Base 2 was compared with the penetration of 1% sulfanilamide from a wet pack consisting of several layers of gauze which was kept saturated with a 1% aqueous solution containing 0.1% aerosol. This detergent was used to cause wetting at hair bases and of the oily skin. Uniform results were not obtained without its use presumably because of lack of uniform wetting caused by the presence of the hair which occluded air bubbles. A similar comparison was made between 10% sodium sulfacetimide in Base 2, *versus* 10% aqueous solution containing 0.1% aerosol. The results are seen in Table 4.

As expected, removing the barrier of the intact skin increases the absorption of both sulfonamides, and levels were reached within the short period of 6 hours which far exceeded those found after 3 days application time to intact skin. Moreover, concentration of sulfonamide had a marked effect on skin absorption in contrast to intact skin. This indicates that in practical use, concentration would be an impor-

tant factor where injured areas are treated, but not for relatively unbroken, cornified or scarified areas.

TABLE 4.—PENETRATION OF SULFANILAMIDE (SNA) AND SODIUM SULFACETIMIDE (NaSAC) INTO THE INTACT AND INJURED SKIN OF GUINEA PIGS FROM AN OINTMENT AND FROM WET PACKS

Vehicle		1% SNA Av. mg. SNA per 100 gm. skin, after 2 hrs.	1% SNA Av. mg. SNA per 100 gm. skin, after 6 hrs.	10% SNA Av. mg. SNA per 100 gm. skin, after 2 hrs.	10% SNA Av. mg. SNA per 100 gm. skin, after 6 hrs.
Ointment base 2	Normal skin	1.2	1.6	1.9	3.6
	Injured skin	4.1	5.2	10.9	25.8
Water + 0.1% aerosol	Normal skin	1.8	2.8		
	Injured skin	30.4	28.9		
		1% NaSAC		10% NaSAC	
Ointment base 2	Normal skin	1.5	3.2	2.0	4.5
	Injured skin	5.2	7.1	26.4	41.0
Water + 0.1% aerosol	Normal skin	..	..	3.2	7.4
	Injured skin	..	..	252.0	288.0

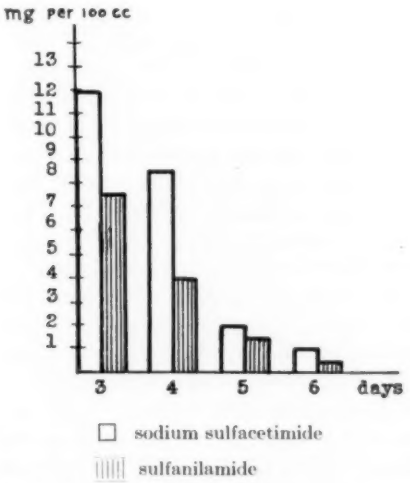

FIG. 1.—Retention of sulfonamides by guinea pig skin. One per cent sodium sulfacetimide (NaSAC) and 1% sulfanilamide (SNA) in ointment base 2 applied for 3 days, then removed. Ordinates show mg. total sulfonamide per 100 gm. skin after 3, 4 and 5 days from the time of the first applications.

6. *Skin Sulfonamide Retention.* One per cent sodium sulfacetimide and sulfanilamide in Base 2 were applied twice daily for 3 days, after which time the skin was washed as previously described. Biopsies were performed after 3, 4 and 5 days from the time of the first application, in order to determine the degree of skin retention of sulfonamide after the external reservoir was removed. The results are seen in Figure 1. Each histogram represents the average of 3 animals per experiment and 15 tissue determinations per point.

It is seen that the skin concentrations drop to therapeutically negligible levels after the 5th day, in both cases, even though the

original sodium sulfacetimide level was higher than the sulfanilamide level. No studies of this nature were deemed necessary in injured skin, as retention would be very small. Hawking[5] has made such studies, using different methods. Goodwin and Findlay[3] have also studied absorption of locally applied sulfonamides by experimental wounds.

Discussion. Several workers have investigated the diffusion of various sulfonamide mixtures out of certain bases, such as emulsions, resins, jellies, pastes, creams and the like, into agar and into flowing water (Waud and Ramsay,[13] Fuller *et al.*,[2] Strakosch and Olson[12] and others). The results of these studies are more applicable to the diffusion of sulfonamides into open wounds than into intact skin, as has been borne out by the work of Fuller *et al.*,[2] who has studied the absorption and retention of sulfonamides in experimental wounds. But such studies are not as applicable to a study of penetration into normal intact skin, and probably so even in injured skin, since the skin barrier cannot be regarded as a sample aqueous or lipid phase.

For this reason we believed that the only logical approach to the problem of skin penetration by sulfonamides was by direct *in vivo* experiments, analyzing skin biopsies for total sulfonamide.

Many workers have used either water-in-oil or oil-in-water emulsion bases for incorporation of certain sulfonamides to be used in skin conditions, usually recommending on theoretical grounds only, oil-in-water bases. The present studies show no effect of the type of base, under the experimental conditions described. The increased interest in the topical application of the sulfonamides, especially in ointment form, is manifested in the numerous preparations which have been advocated. Since various workers have recommended not only different sulfonamides in different bases, but also various concentrations of drugs to be incorporated, the resulting confusion has been great. The literature on sulfonamide ointments is too extensive to be reviewed at this time, although reference may be made to Spink's new edition on sulfonamides,[10] in which topical and dermatologic uses of sulfonamides are discussed, and in Kalz and Prinz' paper[7] in which the literature is reviewed.

The lack of effect of concentration of sulfanilamide,[11] and of sulfadiazine and sulfathiazole on penetration into intact skin suggests that an unnecessary expense may have been associated with the use of higher concentrations in cases in which the skin barrier is relatively intact.

The lack of effect of the type of emulsion base suggests, in confirmation of some of Fuller's *et al.* results,[2] that caution be exerted in extending theoretical deductions or *in vitro* data, to *in vivo* conditions.

Sodium sulfacetimide gave the best penetration into intact skin, suggesting further consideration of this sulfonamide, which is widely used in England, under the trade name of "Albucid soluble" (Schering), even at concentrations of 5% topically applied to the eye.

The fact that removal of the epithelial barrier by injury increased the effect of sulfonamide concentration on absorption by the skin, sug-

gests that higher concentrations be used in cases in which skin lesions have more extensively removed the skin barrier. Hawking[3] and Fuller *et al.*[2] have recommended the use of microcrystalline sulfathiazole or sulfadiazine in cases in which a more protracted absorption is desired and where wet packs are not called for, and the use of water-in-oil bases for ointment application where more protracted absorption is desired.

Summary. 1. *In vivo* experiments on guinea pigs and humans have been performed, to determine the penetration of sulfonamides from various vehicles, into the skin. Skin biopsies were analyzed for total sulfonamide concentration after varying times of applications.

2. Sulfanilamide,[11] sulfathiazole and sulfadiazine, in a comparable base at comparable concentrations and times of application, gave comparable tissue levels, demonstrating no difference in penetration into intact skin. Sodium sulfacetimide ("Albucid soluble"), on the other hand, gave greater penetration after a 3 day application time, than the sulfonamide bases tested.

3. Increasing the concentration of sulfonamide in comparable ointment bases did not increase the absorption by the intact skin of sulfanilamide,[11] sulfathiazole and sulfadiazine. Even sodium sulfacetimide showed only a slight effect of concentration.

4. Increasing the time of application increased the skin absorption of sulfonamide in all cases, especially of sodium sulfacetimide.

5. Of 7 ointment bases examined, 2 oil-in-water and 5 water-in-oil emulsions, the type of emulsion had no effect on the absorption of sulfonamide by the skin, including the sodium sulfacetimide. One water-in-oil emulsion, Base 2, was superior to the others tested.

6. An ointment containing a solubilizer and a wetting agent in greater amounts than in the other bases studied, did not give better absorption of sulfathiazole by the skin than the other bases.

7. Injured skin absorbs much greater amounts of sulfonamides from ointments than intact skin. Sodium sulfacetimide is especially pentrating into injured skin.

8. Injured skin absorbs sulfonamides from wet packs to a much greater extent than from ointments.

9. Some experiments on the retention of sulfonamides by the skin after termination of application, are reported. Negligible levels are encountered after 5 days.

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GASTROPHOTOGRAPHY IN NATURAL COLORS IN CONJUNCTION WITH GASTROSCOPY*

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Some gastrophotographic studies in natural colors, which were made in conjunction with gastroscopy, have been published in a preliminary report.[2] This investigation has been continued further in a series of patients who presented diagnostic and therapeutic problems.

Clinical Study. Altogether 41 patients were studied: 27 males and 14 females. Their ages ranged from 21 to 77 years. The gastroscopic findings in these patients were as follows: a gastric ulcer in 9 patients; carcinoma of the stomach in 14; hypertrophic gastritis in 8; chronic gastritis, in which the superficial type predominated, in 4; deposits of barium sulfate particles adherent to the mucous membrane of the stomach in 1 patient (E. S. whose case report will be described); no gastric lesions in 5 patients. The latter were studied because 2 of the patients had Roentgen ray evidence of duodenal ulcer with pyloric obstruction; another patient, C. W., who had a gastro-enterostomy performed 25 years ago, was admitted for a gastric hemorrhage; 1 patient, W. H., had a questionable Roentgen ray diagnosis of a gastric ulcer; the 5th patient, M. R., had Roentgen ray evidence of a prepyloric ulcer (this case report will also be described).

Method of Procedure. The method of procedure was as follows: After the patient had been gastroscoped with the Wolff Schindler flexible gastroscope, the gastric area which was the site of interest was noted. The distance from the incisor teeth to the depth to which the gastroscope had been introduced was outlined on the flexible tube to which the Gastro-Photor camera was attached. The latter was then inserted to this depth. The photographs, which were taken on Kodachrome film, were developed and enlarged. The endoscopic and photographic studies, in natural colors, were compared with the operative findings as well as the subsequent clinical course.

Of the 41 patients who were observed, the gastrophotographic studies in 26 (63.4%) corresponded to the endoscopic findings. The gastrophotographic studies revealed the following: a gastric ulcer in 5 patients; carcinoma of the stomach in 8; hypertrophic gastritis in 5; chronic gastritis, in which the superficial type predominated, in 2; barium sulfate particles adherent to the mucous membrane of the stomach in 1; no gastric lesion seen in 5 patients. In 15 (36.6%) of the cases the gastrophotographs did not record the endoscopic findings. Four of these patients were suffering from a gastric ulcer; 6 from car-

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Fig. 1.—K. W. A benign prepyloric ulcer.

Fig. 2.—K. W. Another view of the benign prepyloric ulcer.

Fig. 3.—M. R. Gastrophotograph of gastroscopic view, which appears to be the pyloric outlet, but which actually is beyond the field of vistalization. The opening seen in the photograph represents the end of a canal in which there was a carcinoma.

cinoma of the stomach; 3 from hypertrophic gastritis, and 2 from chronic gastritis in which the superficial type predominated.

As was illustrated in the preliminary report,[2] the normal mucous membrane and malignant lesions of the stomach were definitely outlined. They were also clearly seen in the gastrophotographs in this study. Six of the 8 patients with carcinoma of the stomach came to operation. In 4 of these the lesion in the resected part of the stomach had the same color and appearance which were observed in the endoscopic examination and in the gastrophotographs. In 2 of the patients who were operated upon, the lesion appeared to be grayish white in the resected specimen, while in the gastroscopic and gastrophotographic studies, the carcinoma seemed to be definitely greenish in color. This difference in color can be explained on the basis that there was a regurgitation of bile during the endoscopic and photographic examinations. In one case the gastroscopy revealed that the carcinoma was arising from one point and that the rest of the mucous membrane was intact. This was corroborated by the gastrophotographs, and was further verified at operation. Atrophy of the mucous membrane which was seen in cases of malignancy could be readily identified in the gastrophotographs. In one case the latter showed nodules of a carcinomatous lesion in a part of the stomach which was not seen endoscopically.

In the preliminary report[2] it was stated that benign ulcers of the stomach did not photograph very well. This difficulty has been materially overcome as can be seen in Figures 1 and 2. This was a gastrophotograph of K. W., a 39 year old white woman who had a prepyloric ulcer on the lesser curvature. The patient was treated by means of duodenal alimentation. Three weeks later the patient was again gastroscoped, and at this time the ulcer had healed to such an extent that it was hardly visible. There was not enough of it present to be photographed.

During this study, areas were observed presenting the cobblestone appearance or raised beading of the rugal folds which have been described as typical for hypertrophic gastritis. These fields were clearly seen in the gastrophotographs just as they were observed gastroscopically. Areas of hypertrophic gastritis were seen in cases with and without peptic ulcer. In one case the camera caught the edge of the prepyloric ulcer, with the hypertrophic gastritis contiguous to it and enlarged folds in the rest of the stomach with a normal mucosal pattern.

In one of the photographs, the edge of a bleeding ulcer of the stomach was seen. In addition, raised enlarged folds could be clearly outlined. These rugal folds did not present the appearance of an atrophic or a hypertrophic gastritis. While the folds appeared raised, the mucous membrane was dull and swollen, giving a widespread appearance to it. Gastroscopically the impression was that of hyperplasia and not atrophy or hypertrophy, and hence these areas were termed "hyperplastic gastritis." Maher and her co-workers[1] regarded the presence of hyperplasia (increase in the number of glands and in the size of the gland cells) as essential in the microscopic diagnosis of hypertrophic

gastritis. The endoscopic view of the hyperplastic areas which I observed did not correspond, macroscopically, to that described as hypertrophic gastritis, and as outlined before,[3] it may be misleading to designate them as such. These hyperplastic areas have been seen gastroscopically in benign and malignant lesions of the stomach and in 2 cases of ileitis. In the latter there was definite endoscopic evidence of improvement in the stomach when the inflammatory process in the small intestines subsided. Gastroscopically it is not always possible to differentiate between the hyperplastic areas and possible malignant affections of the stomach.

The combined gastroscopic and gastrophotographic examinations were very helpful in the differential diagnosis between benign and malignant lesions of the stomach. In the photograph the sharp line of demarcation of the benign lesion was clearly outlined as can be seen in Figures 1 and 2. The base of the ulcer appeared as a dark blank space. The contiguous areas around it did not have the atrophic appearance to the mucous membrane which was seen in carcinoma. In the latter there was no sharp line of demarcation and the base of the lesion was irregular in appearance and presented the various colors seen gastroscopically. Furthermore, these lesions as a rule gave the impression that they started "nowhere and ended nowhere."

In this study gastrophotography served another purpose, namely, as a check on the clinical appraisal of gastroscopy both from the standpoint of the procedure and the gastroscopist. The latter may see a certain area and interpret his impression accordingly. If the operative findings do not tally with the endoscopic interpretation, the question arises as to whether the gastroscopist saw the involved area. When, however, a photographic record is made of the gastroscopic findings then there can be no doubt as to whether the involved area was seen. The following case will illustrate this point:

Case Study. M. R., 64 years old, stated that for 10 years she had had periodic attacks of upper right quadrant pain which was diagnosed as biliary colic. Gall stones were demonstrated by cholecystography. She said that for the past 6 months she had felt pain in the epigastrium, which would come on about 1 to 2 hours after meals, was located across the stomach, did not radiate and was relieved by food. Nausea occurred frequently. The patient had lost 10 pounds about 6 months ago, but she had regained 4 pounds the past month. After Roentgen radiation at another institution she was told she had a gastric ulcer. This was corroborated by another roentgenologist who reviewed the films. Gastric analysis revealed HCl 50, acidity 60, blood negative. The stools were negative for blood. The gastroscopic examination revealed what appeared to be a normal pyloric outlet. Gastrophotography corroborated these findings (Fig. 3). The patient was operated upon. Cholelithiasis was found. The surgeon also felt what he thought was an ulcer crater at the pylorus. A resection of the pyloric end of the stomach was performed, which was reported by the pathologist as carcinoma of the stomach (linitis plastica). What was seen gastroscopically proved to be one end of a cicatrized canal in which there was a small carcinoma, starting 0.5 mm. from the pyloric end which was 2.5 mm. wide. The pyloric outlet was beyond the field of visualization, although as stated before, endoscopically and photographically, it appeared that the pyloric outlet was visualized.

Comment. The criticisms leveled against previous attempts to photograph the gastric wall included blind photography, questionable interpretation of the films, and, where the rigid gastroscope was used, the risk involved. Therefore, the combined examinations, using the flexible gastroscope in conjunction with the Gastro-Photor camera and taking the films in natural colors represents an advance in this field.

Of the 41 cases observed in this study, the gastrophotographs corresponded to the endoscopic findings in 26 (63.4%) of the cases. In 15 (36.6%) of the cases the lesion, which was seen gastroscopically, was not recorded in the photographs. In 11 of the 15 patients, the gastrophotographs were more or less blurred or they showed whitish circular areas, characteristic of deposits of mucus. In some of these photographs, parts of the gastric wall were indistinctly visualized. These photographic results can be explained on the following basis: At times during the gastroscopy, especially in the nervous individuals or when the endoscopic examination was prolonged, an excessive amount of secretion accumulated. The hypersecretion, while it did not interfere with a satisfactory gastroscopic view of the lesion, was sufficient to prevent a photographic record of it. If the camera dipped into a mucous lake, the gastrophotographs were partially or completely blurred. Even if the camera did not strike one of these areas, but if the lesion was sufficiently covered with mucus, the whitish circular areas, mentioned above, were recorded but the lesion was not seen. In 4 of the 15 patients, the gastric wall was clearly outlined but the lesion was not visualized. In 2 of these patients, the subjects changed their position just as the photographs were being taken, thereby probably shifting the camera to another field and, in 2 of the patients there probably was some error in calculating the depth of the distance to which the camera was inserted.

In this study, the combined gastroscopic and gastrophotographic examinations proved to be of diagnostic aid. In doubtful cases in which a definite clinical or Roentgen ray diagnosis could not be made, the additional diagnostic data were very valuable. Gastrophotography also served as a check on gastroscopy and the gastroscopist. The actual part seen was recorded and therefore any discrepancy in the preoperative and postoperative findings could not be ascribed solely, to the gastroscopist's interpretation, but also to the limitation of the procedure, as was illustrated in the above case report and Figure 3.

At the present time the subject of chronic gastritis is a controversial issue. Schindler has repeatedly emphasized its clinical importance and recently has published his histopathologic study on this subject.[5] Ruffin,[4] again, stated that chronic gastritis is an uncommon affection which does not give rise to a recognizable clinical picture. Therefore, if we can obtain gastrophotographs in conjunction with the gastroscopy, then it may be possible to obtain more unanimity as to what is the endoscopic picture of gastritis. A photographic record of the gastroscopic findings will be much more convincing than the interpretation of different gastroscopists looking at similar fields.

The importance of seeing the gastric wall before photographing it, the avoidance of blind photography, cannot be overemphasized. This was illustrated in the following case:

Case Study. E. S., 43 years old, had a gastric ulcer and lues. By gastroscopy, whitish areas which at first could not be identified, but which looked like barium sulfate particles, were seen adherent to the mucous membrane in the various parts of the stomach. A gastrophotograph of these whitish areas was obtained. It seems that the patient had been Roentgen rayed 2 days before the gastroscopy. The intern was instructed to lavage the patient's stomach, before the endoscopic examination, but forgot to do it. Hence, there was still barium in the stomach. This gave the photographic impression that a widespread tumor was present. If we had looked at the photograph, without seeing the gastric wall, before the picture was taken, an erroneous photographic diagnosis of malignancy could have easily been made, especially since the Roentgen ray examination showed a large gastric ulcer, in which the possibility of malignancy could not be ruled out.

Summary. Gastroscopy with the flexible instrument, in conjunction with gastrophotography in natural colors, was utilized in 41 patients. In 26 (63.4%), the photographs actually depicted what was seen endoscopically. This comparatively combined safe examination serves as a record of the gastroscopic findings, which enhances the endoscopic examination on one hand, and illustrates its limitations on the other.

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BLOOD STUDIES IN THE AGED

Part II. The Leukocytes in the Aged Male and Female

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In Part I of this study, we reported our findings regarding the various hematologic constants in which the erythrocytes were concerned in normal subjects past the age of 65 years.[4] The present study treats the observations made upon a group in the same age range and reporting the total and differential leukocyte counts.

Experimental Study. The same individuals that were described in Part I[4] of this study were used, with the leukocyte counts being done simultaneously with the erythrocyte studies. For the enumeration of the total number of white cells, a Spencer "Bright-line" Hemocytometer was used, which had

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been certified by the U. S. Bureau of Standards, the blood having been diluted in a certified pipette. As the diluting fluid, a 2% solution of acetic acid colored slightly with methyl violet was used. Counts were made in duplicate from each of the two certified pipettes and averaged.

The differential counts were done on blood smears which had been made on glass slides that were kept in chromic acid mixture, washed in distilled water, rinsed in alcohol, and dried over a hot plate. The smears were air-dried, and stained with Wright's stain for 1 to 2 minutes after which a buffer solution of phosphates at pH 6.7 was added until a metallic scum formed upon the surface of the stain. This was permitted to stand for 5 or 6 minutes and then poured off. The slides were then washed with water and air-dried. A total of 500 leukocytes were observed in different sections of the smear and the per cent of each type calculated.

The results of both the total leukocyte counts and the differential counts are to be seen in Table 1.

TABLE 1.—AVERAGE DETERMINATIONS OF TOTAL LEUKOCYTE AND DIFFERENTIAL BLOOD GROUPS BY AGE GROUPS

Age group	No. in group	WBC range in thous.	Av. WBC	Neutrophils				Av. lymphos.	Av. monos.	Av. eos.	Av. basos.
				Av. meta-myelo-cytes	Av. stab forms	Av. 2-lobed forms	Av. seg-mented forms				
				MALES							
65–69	4	5.4–10.2	7.92	0.2	3.5	10.3	49.0	35.2	0.7	0.6	0.5
70–74	6	7.6–11.8	9.16	0.2	6.2	7.5	48.5	34.4	1.6	1.1	0.5
75–79	20	5.0–10.7	7.34	0.3	4.1	6.5	54.0	31.5	1.7	1.4	0.5
80–84	13	7.2–10.2	8.57	0.0	5.3	5.5	50.4	35.2	2.0	1.3	0.3
85–89	5	5.1–10.3	8.30	0.0	2.8	9.6	55.4	28.8	2.0	1.0	0.4
90–94	2	8.7–12.0	10.40	0.0	7.5	7.5	53.5	25.5	1.5	3.5	1.0
				FEMALES							
65–69	4	5.9–9.0	7.60	0.0	4.8	4.6	51.7	36.0	1.2	1.2	0.5
70–74	7	6.6–9.1	7.74	0.1	2.4	4.0	57.6	33.3	1.1	1.0	0.5
75–79	28	6.2–11.1	8.41	0.1	4.0	8.5	49.6	33.8	2.0	1.6	0.4
80–84	3	5.0–10.2	7.23	0.3	3.0	5.3	56.2	32.3	1.6	1.0	0.3
85–89	4	7.9–11.0	9.12	0.0	4.7	4.5	51.0	37.0	1.2	1.4	0.2
90–95	3	6.0–8.4	7.43	0.0	2.6	8.6	51.5	33.8	2.1	1.1	0.3
104	1	...	6.85	1.0	0.0	13.0	32.0	31.0	1.0	2.0	0.0

Discussion. Total white blood counts and differential leukocyte counts were performed on a group of 100 normal aged men and women. Values for the total leukocyte counts for the males ranged from 5000 to 12,050 per c.mm. (mean value, 8330 cells per c.mm.), while for the females the maximum and minimum values for the total leukocyte counts were 11,100 and 5050 respectively (average 8170 cells per c.mm.).

Miller,[3] in 1939, studying 160 men past the age of 60 years and assumed to be normal, found the total white blood cell count to have varied from 4000 to 13,000 cells per c.mm. (average, 7700). (Unfortunately the same type of study was not done by this author for females.)

Values for the total leukocyte counts in normal young adults may be considered to lie between 5000 and 10,000 cells per c.mm.[7] Since 98% of our total counts as well as the majority of those of Miller fall within these limits, we may assume that the total number of leukocytes in the circulating blood does not vary beyond physiologic diurnal

variation at the individual ages. It may be seen from Table 2 that the average values for the differential counts likewise seem to fall within the commonly accepted physiologic normal values.

For young adults, however, Osgood[5] reported that lymphocytes average 37.8%. Dobrovici[1] reported 20% lymphocytes and 5.4% monocytes in studying the blood of 11 persons from 67 to 81 years of age, while Étienne and Perrin[2] found the lymphocyte and monocyte percentages to have been 24.8 and 5.7 respectively in 27 persons past 80 years of age. Our lymphocyte counts average somewhat higher than these values, namely 33.6%. The percentage of monocytes (2.2%) in our subjects was found to be lower than the values reported by the aforementioned 2 writers.

Referring to Table 2, it may be seen that although there is a difference in the mean values for the various findings between the males and the females, it is only in the case of the total white counts that this difference becomes statistically reliable. The difference between the means divided by the square root of the sum of the squares of the probable errors is greater than 6 only in this case. (The value "6" represents the minimum value for truly significant differences.[6])

TABLE 2.—AVERAGE VALUES AND COMPUTATION OF STATISTICAL DIFFERENCES BETWEEN MALES AND FEMALES

	Mean value, male	Mean value, female	σ, male	σ, female	P.E., male	P.E., female	$\frac{M_M - M_F}{\sqrt{PE_M^2 + PE_F^2}}$
Total leukocytes per c.mm.	8330	8170	1600	1355	1078	911	13.50
Stab forms	5.1	4.2	2.8	2.4	1.90	1.6	0.36
Two-lobed forms	7.5	7.7	3.0	3.8	2.04	2.5	0.62
Mature polymorphonuclear neutrophils	52.7	5.3	4.7	1.4	3.20	1.0	0.89
Lymphocytes	33.5	33.8	6.4	6.5	4.30	4.4	0.49

P.E. = Probable Error.
σ = Standard Deviation.
M_F = Mean Female Value.
M_M = Mean Male Value.

$\frac{M_M - M_F}{\sqrt{PE_M^2 + PE_F^2}}$ = Criterion for significant difference.

Thus it may be concluded that aged females, in general, have a total white blood cell count that is slightly lower than that of aged males. The distribution of the various types of leukocytes in the peripheral blood of males is not materially different from that shown by females in the same age group. Furthermore, the normal values reported in the literature as well as in the textbooks for young adults seem to hold for the case of aged individuals.

Conclusions for Part II. 1. Total leukocyte counts and differential counts were performed on a group of 50 normal aged males and 50 aged females.

2. The females showed a statistically reliable difference in the total leukocyte counts from those of the males.

3. The differential blood counts of the males and the females showed no reliable differences.

4. The values reported elsewhere for normal values in younger adults may be assumed to hold for the case of aged individuals.

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THE EFFECT OF MYXEDEMA UPON HEMOPOIESIS IN LEUKEMIA AND RELATED DISORDERS

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There are many publications dealing with the rôle of the thyroid in erythropoiesis. It has been shown[3,9,10,17] that anemia is a frequent finding in myxedema; and there is abundant evidence[6,18] to indicate that the abolition of the thyroid gland depresses erythropoiesis. The reports of the effect of thyroid on myelopoiesis and lymphopoiesis are scanty. In 1934 Dameshek[2] described the improvement in a case of chronic lymphatic leukemia after total thyroidectomy. The following year Witts[19] reported that total thyroidectomy produced no beneficial clinical or hematologic change in chronic lymphatic leukemia. It therefore seemed advisable to investigate the effects of myxedema on hemopoiesis.

Clinical Material and Methods. The cases studied included polycythemia vera (2 cases), erythroleukemia (3 cases), chronic myeloid leukemia (2 cases) and chronic lymphatic leukemia (2 cases). Of this series, 3 cases were considered unsuitable for study because of the short postoperative survival periods.

A complete hematologic survey, including sternal bone marrow examination, was made in each case prior to and after removal of the thyroid. The method used for obtaining and studying these marrows is described by Limarzi.[7] The basal metabolic rate, blood volume estimations and blood chemistry including cholesterol, calcium, phosphorus, serum proteins and uric acid were taken before and repeatedly following thyroidectomy.

All thyroidectomies were performed by the same surgeon (L. S.). After operation the patients were allowed to develop a myxedematous

state as demonstrated by dry, coarse skin, puffiness, heat intolerance, depressed basal metabolic rate and elevated blood cholesterol.

Polycythemia Vera and Erythroleukemia. A case of polycythemia vera previously reported[8] has been followed for the past 7 years. Prior to thyroidectomy the patient's complaints were headache, dizziness, fulness in the head, flushing of the face with cyanosis of the lips, hands and face, weakness, dyspnea, nausea and occasional attacks of vomiting. Headaches persisted for a few months after surgery. Within 3 months she commenced to develop signs and symptoms of hypothyroidism. Two years after the removal of the thyroid this patient presented all the findings of myxedema. The basal metabolic rate was −28%, blood cholesterol−250 mg. per 100 cc. blood and she complained of marked fatigue, edema of the eyelids and ankles, dry, thick skin and a persistent sensation of coldness.

It will be noted (Table 1) that the blood picture has changed markedly. The hemoglobin, erythrocytes and hematocrit have dropped to less than half of the preoperative values. The total blood volume has decreased from 10,706 to 3790 cc. The mean corpuscular volume has increased to 103.7 cu.μ and the mean corpuscular hemoglobin to 36.1 $\mu\mu$g. Thus, we are now dealing with a macrocytic, hyperchromic anemia. The leukocytes, differential blood pattern (Table 2) and platelets were not appreciably altered.

The bone marrow in polycythemia vera reveals a hyperplasia of all the cells. Qualitatively there is a marked erythroid immaturity and normal myeloid and megakaryocytic elements. Following thyroidectomy there is a quantitative decrease in the number of marrow cells while qualitatively the bone marrow is unchanged.

The patient was then placed on thyroid extract. During the next 4 years she was reasonably free of her preoperative symptoms. However, she then began to experience recurrence of headaches and dizziness, and examination of the blood showed a hemoglobin of 17 gm. and an erythrocyte count of 7,800,000. Her symptoms were relieved by repeated venesections. Since then she has taken thyroid extract intermittently and has been able to pursue her routine duties. At times the myxedematous symptoms become pronounced because of failure of the patient to adhere to the dosage of thyroid extract recommended.

Three cases of erythroleukemia were studied. All of the patients presented similar hematologic findings, namely, increased hemoglobin, erythrocytes and leukocytes, and an immaturity of the granulocytes (Tables 1 and 2). In erythroleukemia, which is probably a variant of myeloid leukemia with the added feature of erythremia, the sternal marrow presents a quantitative increase in all cells with a marked myeloid immaturity by virtue of many more neutrophilic myelocytes and myeloblasts than is usually seen in cases of chronic myeloid leukemia or polycythemia vera. There is a marked erythroid immaturity and a pronounced increase in the number of megakaryocytes in various phases of development. After removal of the thyroid, two of the cases of erythroleukemia responded with a considerable depression

TABLE 1.—BLOOD AND LABORATORY FINDINGS BEFORE AND AFTER TOTAL THYROIDECTOMY

TABLE 1.—BLOOD AND LABORATORY FINDINGS BEFORE AND AFTER TOTAL THYROIDECTOMY

Cases	Hemoglobin (gm.)	Erythrocytes (mill.)	Hematocrit (%)	Mean corpuscular volume (cu.μ)	Mean corpuscular hemoglobin (μμg.)	Platelets (number)	Total blood volume (cc.)	B.M.R. (%)	Blood cholesterol (mg./100 cc.)	Date of thyroidectomy
Polycythemia vera (E. A.)										
Before (8/5/35)	21.5	8.62	79.0	92.0	24.8	Normal	10,706	+33	119	8/16/35
After (9/3/37)	11.5	3.18	33.0	103.7	36.1	Normal	3,790	−28	250	
Erythroleukemia (N. A.)										
Before (5/13/39)	19.2	6.30	55.0	87.0	30.0	Normal	5,816	+42	151	5/15/39
After (3/15/40)	17.5	5.46	55.0	101.0	32.0	Normal	7,149	−12	200	
Erythroleukemia (J. K.)										
Before (1/23/38)	22.0	7.75	74.0	95.4	28.4	Normal	9,233	+40	122	2/9/38
After (5/26/38)	16.5	4.26	47.0	110.0	38.0	Reduced	8,711	− 5	147	
Erythroleukemia (K. H.)										
Before (7/22/36)	14.2	7.56	52.0	68.7	18.7	Increased	4,982	+51	139	8/17/36
After (9/24/37)	8.0	3.57	28.5	80.0	22.0	Markedly increased to normal	4,020	−12	250	
Chronic myeloid leukemia (A. S.)										
Before (4/9/38)	15.0	4.68	44.5	93.0	32.0	Normal	...	+28	149	4/18/38
After (3/23/39)	7.8	2.62	27.0	103.0	29.0	Reduced	...	− 6	226	
Chr. lymphatic leukemia (L. N.)										
Before (9/3/38)	10.0	4.09	32.0	80.0	24.2	Normal	...	+35	200	9/15/38
After (8/7/40)	6.7	2.58	16.0	61.0	26.0	Markedly reduced	...	+11	217	

TABLE 2.—LEUKOCYTES AND DIFFERENTIAL BLOOD PATTERN (%) BEFORE AND AFTER TOTAL THYROIDECTOMY

Cases	Leukocytes (thous.)	Myeloblasts	Myelocytes	Metamyelocytes	Stab forms	Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes	Reticulocytes (%)	Date of thyroidectomy
Polycythemia vera (E. A.)												
Before (8/5/35)	6.7	..	..	..	..	78	..	..	20	2	0.8	8/16/35
After (9/3/37)	5.0	..	..	..	..	64	4	3	25	4	1.5	
Erythroleukemia (N. A.)												
Before (5/13/39)	25.5	..	6	5	26	37	9	10	6	1	1.9	5/15/39
After (3/15/40)	43.0	1	10	9	49	9	7	9	4	2	2.0	
Erythroleukemia (J. K.)												
Before (1/23/38)	15.0	..	..	9	..	69	3	2	15	2	3.2	2/9/38
After (5/26/38)	39.0	..	3	15	10	57	2	1	11	1	3.5	
Erythroleukemia (K. H.)												
Before (7/22/36)	21.2	..	..	..	10	80	..	..	5	5	1.5	8/17/36
After (9/24/37)	17.5	..	..	1	34	41	..	3	16	5	0.6	
Chr. myeloid leukemia (A. S.)												
Before (4/9/38)	115.0	4	23	31	..	33	2	2	3	2	1.0	4/18/38
After (3/23/39)	33.1	8	31	14	15	17	3	7	2	3	2.8	
Chr. lymphatic leukemia (L. N.)												
Before (9/3/38)	150.0	..	..	..	..	6	1	..	91	2	0.5	9/15/38
After (8/7/40)	400.0	..	..	..	..	2	1	..	97	..	0.5	

of the hemoglobin and erythrocytes. The third case (N. A.) did not show much change in the hemoglobin and erythrocyte estimations in spite of an existing myxedema. In 2 of the patients (N. A. and J. K.) the anemia was macrocytic and hyperchromic in character. Postoperatively all of the cases showed a progressive leukocytosis and immaturity of the granulocytes, many normoblasts and a variable change in the number of blood platelets.

Before surgery the patient (K. H.) had platelet counts in excess of 1,000,000. These platelets presented alterations in size and shape. The removal of the thyroid induced a "megakaryocytic crisis" in the bone marrow manifested by a rise in the platelet count to 2,500,000 with abnormalities in size and shape of the platelets and megakarocytic elements in the peripheral blood. Three years after operation normal platelet counts were obtained. Except for a moderate decrease in the number of immature erythroid cells the bone marrow remained unchanged.

Chronic Myeloid Leukemia. A case of chronic myeloid leukemia was followed for 1 year after thyroidectomy. Hemoglobin and erythrocytes (Table 1) decreased progressively and 10 months postoperatively they were approximately half of the initial counts. The mean corpuscular volume increased from 93 to 103 cu.μ. The total white cell count dropped from 145,000 to 90,000. Because of progressive enlargement of the spleen several Roentgen ray treatments were administered. Following this, white cell counts of 33,000 to 50,000 were obtained. The differential blood smear (Table 2) prior to removal of the thyroid was typically that of chronic myeloid leukemia (myelocytic-metamyelocytic). The immaturity increased during the remainder of the follow-up study.

The bone marrow in chronic myeloid leukemia consists of an uncontrolled hyperplasia of normal appearing myeloid cells with a depression of erythropoiesis and megakaryopoiesis. Following thyroidectomy, the myeloid immaturity in the bone marrow was increased. The erythroid and megakaryocytic elements were greatly reduced.

Chronic Lymphatic Leukemia. A man with chronic lymphatic leukemia was under observation for 2 years after removal of the thyroid. An appreciable diminution in the hemoglobin and erythrocytes was obtained at this time. The total white cell count had increased from 150,000 to 400,000 with no essential alteration in the differential blood pattern.

The sternal marrow in chronic lymphatic leukemia is overrun by large numbers of small lymphocytes, similar to those seen in the peripheral blood. There is an almost complete disappearance of nucleated red cells and megakaryocytes. Complete ablation of the thyroid gland does not produce any significant change in the bone marrow.

Additional Laboratory Findings. A gastric analysis before removal of the thyroid and after development of myxedema was performed in 3 of the cases (E. A., J. K., K. H.). No significant difference in the

degree of acidity was noted. In 2 of the cases studied, the absence of free acid was determined even after histamine stimulation.

Except for the cholesterol the blood chemistry was not appreciably changed. In all cases the blood cholesterol (Table 1) was found to be increased after surgery. Two of the patients exhibited symptoms and findings of postoperative tetany with blood calcium values of 5.5 and 6 mg. per 100 cc. of blood.

Discussion. In a comprehensive review of the literature on the peripheral blood in thyroid disturbances, Bomford[1] is of the opinion that the anemia in myxedema is a physiologic adaptation on the part of the red cell to a diminished need of the tissues for oxygen. He points out that the anemias found with myxedema can be divided into 3 types, (1) hyperchromic macrocytic, (2) hypochromic and (3) Addisonian hyperchromic. Following total thyroidectomy for the treatment of congestive heart failure and angina pectoris, Stern and Altschule[16] noted the development of a macrocytic, hyperchromic anemia. Jones[5] in a study of the sternal bone marrow in myxedema and hyperthyroidism found a normocytic, hypochromic anemia in his series of hypothyroid cases. Sharpe[15] working with thyroidectomized rabbits obtained an anemia characterized by a definite macrocytosis and hyperchromia. This change was not found clinically and the author believes this discrepancy may be due to the amount of functioning thyroid tissue in the spontaneous cases of myxedema. Kunde, Green and Burns[6] produced experimental cretinism in rabbits by total extirpation of the thyroid. Four to 6 months after thyroidectomy a macrocytic anemia was found.

Of the 6 patients in this series completely studied, 4 developed a macrocytosis. Three of these cases had an associated hyperchromia. A microcytic, hypochromic anemia was observed in a case of erythroleukemia and in chronic lymphatic leukemia. The macrocytosis found postoperatively is similar to the results of Sharpe,[15] Stern and Altschule,[16] and Kunde, Green and Burns.[6] The macrocytic anemia or macrocytosis following thyroidectomy in these hemopoietic disorders was not associated with a megaloblastic bone marrow nor with a megalocytic, pernicious anemia blood pattern peripherally.

The induced myxedema did not influence the leukocytes or the blood pattern in polycythemia vera. Increased leukocyte counts and a greater immaturity of the granulocytes were found after thyroidectomy in erythroleukemia. It is sometimes difficult to distinguish between erythroleukemia and polycythemia vera. The erythremia, leukemic blood picture, thrombocythemia with atypical blood platelets and megakaryocytic elements and the leukemic involvement of the spleen, liver and lymph nodes serves to separate these cases from polycythemia vera. Occasionally cases of polycythemia vera with an overactivity of the leukogenic and megakaryogenic tissues may result in granulocytic immaturity and an increased number of normal and atypical platelets and megakaryocytic elements in the peripheral blood. A number of authors[11] have expressed the opinion that leukemia and

polycythemia vera are related diseases. On the other hand Naegeli[12] considers cases of erythremia which subsequently show signs of myelogenous leukemia as examples of myeloid leukemia at a stage before anemia has appeared. Harrop[4] and Reznikoff, Foot and Bethea[14] believe that polycythemia vera and leukemia are not related disorders.

In contrast to the report of Dameshek[2] the case of chronic lymphatic leukemia followed in this series did not benefit by total removal of the thyroid. The anemia became more profound, the leukocytes increased approximately 3 times their initial number and the differential did not change appreciably.

Naegeli[12] considered leukemia to be a disease produced by hormone disturbance. According to Oswald[13] no gland of internal secretion, however greatly disturbed, shows a blood picture which might even resemble leukemia. From the results of this investigation it would seem that the leukemic processes (myeloid and lymphatic) were not affected by total thyroidectomy. The case of myeloid leukemia survived for 1 year after surgery and the clinical and hematologic pictures with the exception of the myxedema did not appear to differ from that observed in the usual course of leukemia.

Conclusions. 1. Erythropoiesis is depressed in polycythemia vera after a total thyroidectomy and development of myxedema. The anemia is macrocytic and hyperchromic in type. Leukopoiesis is unaffected.

2. In erythroleukemia, myxedema induced a moderate to marked depression in erythropoiesis. The anemia is macrocytic or microcytic in type. There is a stimulation of leukopoiesis. In 1 case, after thyroidectomy there was early a "megakaryocytic crisis" followed later by normal platelet counts.

3. Hemopoiesis in chronic lymphatic and chronic myeloid leukemia is not altered by an induced myxedema.

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AIR-BORNE CROSS-INFECTION IN THE CASE OF THE COMMON COLD

A Further Clinical Study of the Use of Glycol Vapors for Air Sterilization*

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By far the greater part of mild upper respiratory infections probably originate from a virus or from viruses as yet unidentified. For this reason, quantitative determinations under varying environmental conditions of the viricidal effect of glycol vapors upon these disease agents cannot as yet be carried out. However, an essential experimental approach to this problem can be made by investigations of the incidence of mild upper respiratory infections and particularly of the common cold in children confined to bed in a convalescent home under controlled conditions and with the addition of glycol vapor to the air. Such an approach, as outlined in a preliminary report[1] and as carried out at the Children's Seashore House, gave sufficiently encouraging results to warrant a further clinical study. The present report covers the incidence of mild upper respiratory infections over a longer period and with larger groups of children in the same institution under similar environmental conditions.

Clinical Material. In contrast to the preliminary study[1] in which propylene glycol was vaporized continuously in a single ward for a period of over 2 months, a suitable control ward being maintained without glycol vapor, the present study included 6 wards (*i. e.*, 3 wards on each of 2 floors) of the convalescent home over a period from October 1, 1942, to April, 1943, inclusive. In addition to the separation of the children on the 2 floors, each ward on the same floor was separated from the others by long corridors. The wards on the upper floor, located directly above those on the lower floor, had the same size, shape, position, exposure, and window space as those on the lower floor. Although the children with a few exceptions were not allowed out of bed, thus preventing for the most part actual contact between them, the nurses and other personnel frequently visited from ward to ward on the same floor, although they rarely visited from one floor to the other. Toys and books were transferred at times, though not frequently, from bed to bed, inasmuch as some of the beds were placed in contiguous pairs and no particular effort was made to prevent this, except during respiratory episodes in individual patients. Parents and friends visited the patients usually over the week-ends, but such visits became less frequent during the period of the study as the ban on pleasure driving in automobiles became more strict. In addition, contacts

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with family and friends almost ceased during the period of study from mid-January as the result of a quarantine against visitors from the Philadelphia area, where a small epidemic of smallpox occurred. This quarantine was apparently reflected in the incidence of respiratory infections in the control wards (Table 1). The majority of the children were convalescent from rheumatic heart disease, 45 in number, and from orthopedic conditions, 30; while the rest, 30, represented a variety of non-infectious conditions. The ages ranged from 3 to 15 years. The sexes were evenly distributed.

TABLE 1.—THE INCIDENCE OF RESPIRATORY INFECTIONS, CHILDREN'S SEASHORE HOUSE (1942–43)*

Period beginning	Ward						Total cases	
	2A	2B	2C	3A	3B	3C	Controls	Glycol wards
10/9†	0	0	0	6	5	8	19	0
11/2‡	7	6	7	0	0	1	20	1
11/26†	0	2	0	4	8	7	19	2
12/21‡	5	9	6	0	0	1	20	1
1/14†	0	0	..	4	3	..	7	0
2/8‡	3	4	..	0	1	..	7	1
3/4†	0	0	..	4	4	..	8	0

TOTALS AND AVERAGES

Ward condition	Total	Per 3-week period	Per week
Before quarantine	78	6.5	2.2
After institution of quarantine	22	3.6	1.2
Total without glycol vaporization	100	5.5	1.8
Total during glycol vaporization	5	0.28	0.09

Method of Study. The study was divided into 3-week periods of vaporization, separated by 2 to 3 days with no vaporization. The vaporization was continuous for each period on the 3 wards of one floor, while the 3 wards of the other floor remained as a control. Following the 2- to 3-day interval between periods, the 3 wards which had been vaporized became the control wards and the 3 control wards of the previous period became the vaporized wards. Such alternation, with the 2- to 3-day intervals between, occurred throughout the length of the study. The number, nature, and severity of the respiratory infections were recorded during each 3-week period in the 6 wards. The interval of 2 to 3 days was arranged for the purpose of permitting a respiratory infection which was incubating from the previous 3-week period to occur before the succeeding 3-week period started. Such an incubating infection was far more likely to occur from the control than from the vaporized wards, and had the 3-week periods alternated without a 2- to 3-day interval, respiratory infections for which they could not have been considered responsible would have been tabulated as occurring in the vaporized wards.

The method of vaporization of propylene glycol differed from that previously described in that the heat for vaporization was supplied by a small radio resistance unit inserted directly into the propylene glycol which was maintained at a constant level.§ During the greater part of the study, electric fans were placed behind the units for better distribution of the vapor. Units

* Only 3 of these respiratory infections represent a second infection in a child previously infected. The interval between the 2 infections was never less than 5 weeks.

† Glycol vaporized on 2d floor (Wards 2A, 2B, 2C).

‡ Glycol vaporized on 3d floor.

§ The temperature of the heated glycol was kept below 80° C. It is important to avoid high temperatures because of the possibility of producing toxic oxidation products of the glycol.

of this type with electric fans were arranged on stands at the mid-point of the end-walls of each room, approximately 3 feet from the ceiling.

Determinations of the concentration of propylene glycol vapor were made at regular intervals throughout the study[2] (Table 2). As in the previous report, the samples of air were obtained from various points in the room at approximately the level of the patients' heads. Table 2 also indicates the variation in the amount of propylene glycol at such points, with the electric fan both on and off. The amount of propylene glycol vaporized daily was 600 cc.

TABLE 2.—CONCENTRATION OF PROPYLENE GLYCOL VAPOR IN AIR—MG. PER LITER

I. Samples at random, vapor dispensed by fan:

.067	.059
.085	.078
.054	.064
.042	.088
.070	.074
.086	.060

Mean: .069

II. Samples at various parts of ward, without fan:

Near vaporizer	Middle of ward	Far end
.068	.096	.060
.080	.120	.058
.074	.090	.040
.088	.080	.038
.092	.109	.044
.018	.093	.047
Mean: .094	.081	.048

III. Samples at various times after cessation of vaporization:

Hours after cessation of vaporization	Location of sample taken: ¼ length of ward from vaporizer	Location of sample taken: ¾ length of ward
0	.072	.045
	.060	.055
1	.023	.022
2	.033	.020
3	.009	.008

Determinations also were made of the rate of disappearance of propylene glycol from the wards following the cessation of vaporization, in order to afford some general idea of the effect of the exchange of air in the rooms on the concentration of the vapor. Such determinations showed that at the end of 1 hour approximately half of the original concentration of vapor was present; at the end of 2 hours, approximately a quarter was present, and at the end of 3 hours approximately one-eighth was present (Table 2). These determinations were made under the ordinary conditions of activity in the wards and indicate that the turnovers of air were considerably fewer than those to be expected in a more active institution.

Sufficient concentrations of propylene glycol were thus maintained to insure a marked reduction over the entire study in the total bacterial plate counts of the vaporized wards as compared with the control wards (Table 3). In the final period of 3 weeks, triethylene glycol in the concentrations originally suggested by Robertson was vaporized in the 3 test wards. During this and the 2 preceding 3-week periods, 1 of the wards included in the study was closed, chiefly due to the quarantine of the Philadelphia area for smallpox. Such

closure eliminated 2 wards from the latter part of the study, inasmuch as another ward comparable to the closed ward had to be omitted from the final calculations of the incidence of respiratory infections for proper comparison. Triethylene glycol in the concentrations used resulted in an even greater reduction in the few bacterial plate counts made than that resulting from propylene glycol vapor, although the concentration of the latter was maintained at approximately 10 times that of triethylene glycol. Because of the greater heat of vaporization of triethylene glycol, the same apparatus for vaporization could be used for both vapors, with the resulting approximate ratio of concentrations mentioned. The amount of triethylene glycol could be calculated only roughly because of the lack of a satisfactory method of air analysis for the vapor. The temperature of the wards usually was within the range of 68° to 72° F. The relative humidity was not determined in the wards in the earlier periods of the study; while in the later periods it ranged from 30 to 35%. The study was started at a time when the windows were closed for the colder season and was stopped when the windows were again opened for the warmer season.

TABLE 3.—BACTERIAL PLATE COUNTS IN WARDS CONTAINING PROPYLENE GLYCOL VAPOR AND IN CONTROL WARDS

Colonies per Petri plate per hour		Colonies per Petri plate per hour (*Cont'd*)	
Control	Propylene glycol	Control	Propylene glycol
66	13	70	13
85	12	84	12
72	14	72	14
81	17	81	11
89	11	96	11
93	10	84	8
64	12	92	12
68	9	73	14
102	13	86	13
79	11	92	15
83	9	103	16
73	13	84	15
62	14	107	12
59	16	86	14
91	14	—	—
84	19	Mean: 81.3	13.4
68	9		

BACTERIAL PLATE COUNTS IN WARDS CONTAINING TRIETHYLENE GLYCOL VAPOR AND IN CONTROL WARDS

Colonies per Petri plate per hour			
Lower concentration		Higher concentration	
Control	Trieth. glycol	Control	Trieth. glycol
94	12	98	3
76	11	70	4
87	9	103	4
99	10	111	1
103	11	99	0
74	9	79	6
88	11	84	4
94	12	81	2
90	10	94	2
89	13	91	3
93	11	93	1
91	8	86	5
Mean: 89.5	10.6	91.1	2.94

Results. The criteria* used for respiratory infections were the same as indicated in the previous study,[1] with the exception that in a very few instances upper respiratory episodes were included which did not show fever. All such non-febrile episodes were of the type considered to be common colds and were only included on the basis of unmistakably objective signs. Table 4 indicates the total number of respiratory episodes and their division among the 4 categories, *i. e.*, common cold, pharyngitis or sore throat, otitis media, and tracheobronchitis. The difference between the vaporized and the control wards is sufficiently striking to require no statistical support. It will be noted that by far the greatest number of respiratory infections, 79, were classified as common colds. In one of the wards in which a nurse was suffering from a severe common cold during a period of vaporization, only 2 children contracted what appeared to be the same disease, whereas in other instances in several of the wards acting at the same time as control wards without vaporization, common colds appeared to develop in considerable numbers from an infected nurse or from other infected children. The period of quarantine due to the smallpox epidemic in the Philadelphia area started on about February 1. Whether or not this was responsible for the lessening of the respiratory episodes following that date is not clear, and yet the association of the two events is sufficiently close to appear related. The bacterial flora of the nasopharynx were not investigated, largely because there was no sharp epidemic of respiratory infections during the period of study.

TABLE 4.—THE DISTRIBUTION OF THE RESPIRATORY INFECTION BY DIAGNOSIS

Type of infection	Number	
	Control	Glycol
Tracheobronchitis	12	0
Otitis media	2	0
Acute pharyngitis	7	2
Common cold	79	3

Discussion. The striking reduction in common colds in the wards vaporized with propylene glycol is clear-cut evidence of the air-borne spread of the causative agent or agents of the common cold under the environmental conditions of this convalescent home for children. It must be emphasized that the children, with few exceptions, were confined continuously to their beds and the opportunities for direct contact were infrequent. Had direct droplet hits† from sneezing or coughing been factors in the spread of infections, a larger number of respiratory episodes would have been expected in the vaporized wards, since propylene glycol could hardly have prevented this mode of spread.

* A respiratory infection was defined as a clinically recognizable episode with some objective manifestation in addition to fever. Thus a sore throat was included only if it showed an inflamed nasopharynx on examination; a "common cold," or painful ear was included only if a discharge or evidence of inflammation was present, and a cough was included only if productive.

† Obviously the differentiation between direct droplet hits and air-borne droplets cannot be sharp, but is a useful clinical distinction.

The lack of infections from direct droplet hits was also related apparently to the confinement of the children to their beds. A sufficient reduction in the number of cases of pharyngitis and bronchitis was noted in the vaporized wards to warrant the supposition that cross-infections by air-borne bacteria were also limited by the propylene glycol vapor although in the absence of nasopharyngeal cultures this must be considered conjectural. In the instance of 1 nurse who remained on duty in a vaporized ward while suffering from a severe common cold, the opportunities among the children for contact infection or infection from direct droplet hits were considerably increased and apparently resulted in 2 common colds among them. In these 2 instances, the possibility of air-borne cross-infection from the same nurses could not be entirely eliminated.

That sufficient propylene glycol vapor was continuously present in the vaporized wards to reduce markedly the air-borne infective agents is evident from the bacterial plate counts obtained throughout the study. Inasmuch as the virus agents of disease thus far studied have been found susceptible to higher dilutions of the glycol vapors than the bacterial agents, the assumption is warranted that the propylene glycol vapor in the concentrations used inactivated the air-borne agent or agents of the common cold. The relative humidity in the periods tested was near the lower effective range for the antibacterial activity of propylene glycol (35 to 40%). The bacterial plate counts demonstrated that this degree of humidity was sufficient for such activity.

The total daily amount of propylene glycol vaporized would have had to be considerably greater in order to maintain an effective concentration, had not the turnovers of air in the wards been relatively few, as demonstrated by the quantitative determination of propylene glycol over a period of several hours following the cessation of vaporization. The amount of vapor for the purpose desired was not only sufficient by direct analysis but also sufficient according to bacterial plate counts. The effectiveness of triethylene glycol for the prevention of cross-infections was not demonstrated statistically in this study, although the small amount of evidence, as shown in Table 3, was entirely favorable to its value, as also were the bacterial plate counts.

Summary. Propylene glycol was vaporized in wards of a children's convalescent home in bactericidal concentration. The incidence of upper respiratory infection was compared in these wards with that in control wards and found to be much lower. The fact that the great majority of the upper respiratory infections in control wards were common colds provides additional evidence of the viricidal effect of propylene glycol vapor, and may give indirect evidence also of the air-borne transmission of the common cold.

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THE BONE MARROW OF NORMAL DOGS

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In a study of spontaneous lymphomas in dogs, it was necessary to develop a technique for repeated bone marrow studies in the living animal. A review of the literature disclosed no consistent methods or results which could be used for a standard. Alexandrov[1] employed Arinkin's[2] sternal aspiration method in the study of the bone marrow of 12 normal dogs, and calculated the percentage distribution of marrow cells. Stasney and Higgins[6] investigated the marrow of 35 apparently normal dogs immediately after death of the animals by making imprints and sections of the 7th right ribs and the proximal and middle portions of the right femurs. They found only slight variations in the cellular organization from the different sites selected, although their quantitative results differed from those of Alexandrov.[1] This was attributed to the fact that their animals were anemic as reflected by lowered peripheral red cell counts. Mulligan[4] examined paraffin sections and smears of the bone marrow in 35 normal living adult dogs and 4 puppies by resecting portions of the 10th, 11th and 12th ribs under nembutal anesthesia. The smears were made by expressing the marrow from the rib with bone forceps, emulsifying it with plasma from the same animal, and then spreading this mixture on glass slides. His results were similar to those of Alexandrov,[1] and this procedure was suggested for repeated bone marrow studies, as 12 biopsies may be done on an animal if the 7th, 8th and 9th ribs (which are easily accessible) are also used.

In evaluating these techniques for obtaining marrow, Arinkin's[2] aspiration method is the simplest and an unlimited number of successive biopsies can be made upon the same animal. We have applied this procedure successfully in young dogs of medium and large size, but difficulty was experienced in small dogs due to the narrow medullary cavity, and in older dogs due to an increase in density and thickness of the outer layer of compact bone. Ho, Chu and Yuan[3] described a rapid method for the diagnosis of canine leishmaniasis by aspiration of bone marrow from the crest of the ilium. We have used this site successfully in obtaining marrow from animals of all ages and size. In addition to greater accessibility, it has all the advantages of Arinkin's[2] method, as the sternal marrow in the dog can only be aspirated from the upper 4–5 segments.

Material and Methods. The bone marrow was obtained from 10 healthy male and female dogs of different breeds, ranging in age from 1 to 11 years, and which were free from internal and external parasites. The animals were privately owned, and unlike the usual laboratory dog, had been well-fed and not subjected to any previous operative or other experimental procedure.

Examination of the peripheral blood indicated hemoglobin, red, white and differential counts within the accepted normal ranges.

The ilium of the dog is nearly parallel with the median plane of the body. The outer gluteal surface of the wing of the ilium is concave and thin. It is expanded anteriorly to form the crest which is strongly convex, thick, rough and prominent. The wing is bounded dorsally by the tuber sacrale which is thickened and has 2 eminences, and ventrally by the tuber coxæ which has 2 prominences. The tuber sacrale and coxæ together with the crest join to form the outer border of the anterior portion of the ilium.

The technique for marrow puncture is as follows: The animal is held on its side by an attendant or is strapped to the table in that position. Local anesthesia is not required as very little pain is experienced, and it is unnecessary to clip or shave the hair from the intended puncture region. The skin and hair over that area are sterilized with any suitable antiseptic. The anterior border of the ilium is outlined with the fingers of one hand, and a sterile $1\frac{3}{4}$ inches long, 15 to 18 gauge Kaliski or similar type needle with attached stylet is inserted through the skin and muscles into the thickest portion of the crest. The needle is simultaneously pushed and rotated with a screwing movement until the medullary cavity is entered. Occasionally, entrance is recognized by a sudden "give," although this is not usual. When the marrow cavity has been penetrated, the stylet is removed and a dry 10 to 20 cc. syringe is attached to the needle and about 0.1 to 0.2 cc. of the marrow withdrawn. The needle together with the attached syringe is removed from the animal and the drop expelled on a clean glass slide. From this drop, white cell and megakaryocyte counts are done with the same technique as for the white cells of the peripheral blood. Thin smears are made on several clean glass slides and stained with Wright's or May-Grunwald-Giemsa as for peripheral blood smears. Five hundred nucleated cells are enumerated and the percentages estimated for the differential count from the stained smears.

Several precautions must be exercised in obtaining the marrow. Not more than 0.2 cc. should be withdrawn to avoid too great an admixture with blood. As a distinct "give" is usually not felt when the medullary cavity is entered, the needle can easily be pushed completely through the bone. To avoid this, the needle should be directed toward the thickest portion of the crest, the syringe attached to the needle frequently and the plunger withdrawn to determine entrance into the marrow cavity. The bone marrow of the dog coagulates very quickly, requiring rapid execution of the entire procedure. Anticoagulants are not recommended as the fragility of the cells may be increased and a greater number of unidentified cells obtained in the differential count. If the animal is obese, the $1\frac{3}{4}$ inch needle may be too short, so that a longer needle, 2 to 3 inches in length should be used.

Observations. The marrow cells of the dog are similar to those in man, and we have followed the classification of Vogel, Erf and Rosenthal[7] in the identification of the cellular constituents of the dog marrow. The results of the peripheral blood and marrow studies are recorded in Table 1. Our observations indicate that an average of 48.32% of the marrow cells are of the myeloid series distributed as follows: neutrophilic myelocytes (3.76%), non-segmented neutrophils (23.5%) and segmented neutrophils (18.5.%). The myeloblasts, eosinophilic myelocytes and non-segmenters, eosinophils, basophils and heterophils together comprise 2.56%. The erythroid cells average 38.7%, of which the megaloblasts are 1.02%, erythroblasts 2.5% and normoblasts 35.18%. The remaining 12.98% consist principally of lymphocytes which total 9.8% leaving 3.18% for the other classified cells.

In stained marrow smears, occasional agranulocytic myelocytes and polynuclears occur, which are attributed to differences of maturation

TABLE 1.—PERIPHERAL BLOOD AND ILIAL BONE MARROW OF NORMAL DOGS

TABLE 1.—PERIPHERAL BLOOD AND ILIAL BONE MARROW OF NORMAL DOGS

Description	Beagle M 3 yrs.	Cocker F 3 yrs.	Beagle F 1½ yrs.	Collie cross M 4 yrs.	Chow cross M 3½ yrs.	Wire-haired terrier M 11 yrs.	Cocker M 3 yrs.	Fox terrier M 3 yrs.	Beagle M 7 yrs.	Boxer M 7 yrs.	Aver.	Group aver.
Peripheral Blood												
Red cells per c.mm. × 1000	6440	7090	7440	6110	6340	5960	6900	6660	6850	6500	6629	
Hemoglobin (Newcomer method), gm. per 100 cc.	11.6	12.0	11.0	12.8	11.8	12.0	12.7	13.1	12.4	13.1	12.25	
White cells per c.mm. × 100	126	172	175	121	114	100	136	129	142	137	135	
Juvenile neutrophils	2.0	1.0	1.0	...	2.0	1.0	2.0	2.0	1.0	...	1.2	
Bands	5.0	8.0	2.0	3.0	6.0	4.0	4.0	2.0	3.0	4.0	4.1	
Segmented	69.0	78.0	66.0	68.0	59.0	64.0	63.0	71.0	68.0	64.0	67.0	
Eosinophils	3.0	...	7.0	5.0	4.0	5.0	3.0	4.0	3.0	5.0	3.9	
Basophils	1.0	...	1.0	1.0	...	...	...	...	...	...	0.3	
Lymphocytes	17.0	12.0	20.0	21.0	26.0	23.0	27.0	19.0	21.0	21.0	20.7	
Monocytes	3.0	1.0	3.0	2.0	3.0	3.0	1.0	2.0	4.0	6.0	2.8	
Normoblasts (No. per 100 white cells)	...	3.0	2.0	...	...	...	...	1.0	...	...	0.6	
Bone Marrow												
Cells per c.mm. × 1000	317	90	100	110	56	120	95	192	240	128	144	
Megakaryocytes per c.mm.	33	33	22	5	11	11	22	110	132	33	41.20	
Myeloblasts	1.6	0.2	0.2	0.6	0.6	2.0	...	0.2	...	0.4	0.58	
Myelocyte neutrophils	5.4	0.2	1.8	1.4	2.8	7.6	4.2	6.2	3.6	4.4	3.76	
Myelocyte eosinophils	0.8	...	...	0.2	...	...	...	0.6	0.2	0.8	0.26	
Non-segmented neutrophils	22.8	16.2	19.2	29.2	24.4	28.4	22.6	20.2	24.8	27.2	23.50	
Non-segmented eosinophils	0.8	...	...	...	...	...	...	...	...	0.4	0.12	48.5
Segmented neutrophils	17.4	19.0	20.0	23.2	29.6	14.6	16.8	13.0	12.4	19.0	18.50	
Segmented eosinophils	0.4	2.4	...	1.0	2.4	3.0	1.4	2.0	1.0	2.0	1.56	
Segmented basophils	...	...	...	...	...	0.2	...	...	...	...	0.02	
Heterophils	0.2	...	...	...	...	...	...	...	...	...	0.02	
Megaloblasts	2.0	0.2	0.4	0.2	...	1.8	0.2	2.8	1.0	1.6	1.02	
Erythroblasts	2.6	2.8	2.0	1.4	0.8	3.8	3.6	2.4	4.0	1.6	2.50	38.7
Normoblasts	37.0	46.6	38.8	26.4	22.8	29.4	39.8	39.2	43.8	28.0	35.18	
Lymphocytes	8.4	8.2	14.2	7.2	15.2	8.0	10.6	10.0	5.8	10.4	9.80	9.8
Pathological lymphocytes	...	...	0.2	0.2	...	...	...	...	...	...	0.04	
Monocytes	0.4	2.6	1.0	5.2	0.4	0.2	0.6	1.0	0.4	0.2	1.20	3.1
Monoblasts	...	1.0	...	0.4	...	...	...	...	...	...	0.14	
Plasma cells	...	0.6	1.2	2.0	0.4	...	0.2	0.6	1.0	2.2	0.82	
Hematogones	...	...	0.8	0.8	0.6	0.2	...	0.4	0.4	1.2	0.44	
Reticulo-endothelial cells	0.2	...	0.2	0.6	...	0.8	...	1.4	1.6	0.6	0.54	
Myeloid-erythroid ratio	1.18:1.00	0.76:1.00	1.00:1.00	1.98:1.00	2.53:1.00	1.59:1.00	1.03:1.00	0.94:1.00	0.86:1.00	1.73:1.00	1.36:1.00	

rate of the nucleus and cytoplasm.[7] In addition to these agranulocytic forms, there are found granule-free myelocytes, non-segmented and segmented neutrophils that have matured equally as far as the nuclei and cytoplasm are concerned. The criteria for their recognition depends on the nuclear and cytoplasmic characteristics.

TABLE 2.—COMPARISON OF PERIPHERAL BLOOD AND BONE MARROW DATA OF NORMAL DOGS REPORTED BY DIFFERENT AUTHORS

Peripheral blood	*Alexandrov*	*Stasney and Higgins*	*Mulligan*	*Present authors*
Red blood cells per c.mm.	6,335,000	5,000,000	6,760,000	6,629,000
Hemoglobin	100%	No other	14.4 gm.	12.25 gm.
White blood cells per c.mm.	11,260	data	10,700	13,520
Metaneutrophils	0.17	given		
Juvenile neutrophils	...		...	1.2
Stab neutrophils	...		4.2	4.1
Neutrophils	67.23		70.6	67.0
Eosinophils	3.48		4.1	3.9
Basophils	0.06		...	0.3
Lymphocytes	14.30		19.3	20.7
Monocytes	12.30		1.8	2.8
Smudge forms	1.30			
Türck cells	1.00			
Reticulo-endothelial cells	0.02			
Normoblasts (number per 100 white cells)	...	...	...	0.6

Bone marrow	*Sternum*	*Rib*	*Rib*	*Ilium*
Total white cells per c.mm.	...	...	...	144,800
Megakaryocytes per c.mm.	...	...	...	41.20
Myeloblasts	1.20	0.51	...	0.58
Leukoblasts	...	1.89		
Promyelocyte neutrophils	0.90	2.83	1.5	
Myelocyte neutrophils	1.20	8.93	4.7	3.76
Myelocyte eosinophils	0.50	1.15	...	0.26
Metamyelocyte neutrophils	6.70	15.29	10.5	
Metamyelocyte eosinophils	1.60			
Stab neutrophils	...	...	31.0	
Non-segmented neutrophils	...	...	...	23.50
Non-segmented eosinophils	...	...	...	0.12
Neutrophils	35.10	...	3.9	18.50
Eosinophils	1.32	2.85	3.7	1.56
Basophils	0.13	0.05	...	0.02
Granulocytes	...	5.06		
Heterophils	...	0.14	...	0.02
Megaloblasts	...	...	...	1.02
Proerythroblasts	1.90	...	0.5	
Erythroblasts	21.50	...	1.5	2.50
Normoblasts	...	58.98	38.1	35.18
Megakaryocytes	0.10	0.12		
Lymphocytes	8.80	1.24	1.9	9.80
Pathologic lymphocytes	...	...	...	0.04
Monocytes	10.40	...	...	1.20
Monoblasts	...	...	...	0.14
Plasma cells	...	...	...	0.82
Reticulo-endothelial cells	5.10	0.99	...	0.54
Stem cells	...	...	0.6	
Türck cells	0.30			
Hematogones	...	...	...	0.44
Smudge forms	2.60			
Unidentified cells	...	...	2.1	
Myeloid-erythroid ratio	2.08:1.00	0.65:1.00	1.60:1.00	1.36:1.00

The presence of occasional deep blue granules in eosinophilic myelocytes and non-segmenters has been described in man and dog. There appear to be greater numbers of these cells when the smears are stained with May-Grunwald-Giemsa than with Wright's stain.

Comment. Table 2 demonstrates a comparison of our quantitative data of the bone marrow and peripheral blood with that obtained by other investigators. Although the data for the peripheral blood are very similar, this is not true for the bone marrow. In addition to variations in nomenclature, there are differences in the quantitative percentages of the marrow cells. The latter may be due to the animals used as, with the exception of our series, laboratory dogs were employed in all instances.

The myeloid-erythroid ratios in man, rat and the rabbit are greater than one.[6] This is also noted in the dog, but in general there are greater numbers of erythroid cells as compared to myeloid cells than in man and rabbit. The increase in cells of the erythroid series in the dog may be possibly due to the fact that the red cells of the peripheral blood occur in larger numbers, which might necessitate a greater erythroid activity to maintain the normal quota of erythrocytes in the circulating blood.

Reich and Kolb[5] in a recent quantitative study in man found considerable variations in multiple sternal marrow samples taken simultaneously. These observations consequently cast doubt on the accuracy of total cell counts of the marrow. Despite this criticism, we believe such examination aids in distinguishing hypoplastic from hyperplastic centers, particularly when care is exercised in aspirating not more than 0.2 cc. of marrow.

The technique of obtaining marrow from the crest of the ilium is of obvious value when repeated examinations are desirable. The procedure is simple and lends itself to frequent observations of changes in the myeloid and erythroid tissue under normal, diseased and experimental conditions.

Summary. 1. A simple method suitable for repeated biopsies in obtaining bone marrow from the crest of the ilium in living dogs has been described.

2. Data has been given for 10 normal dogs concerning the total number of nucleated cells and megakaryocytes, and the percentage distribution of marrow cells of the ilial bone marrow.

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THE TOXICITY OF PENICILLIN AS PREPARED FOR CLINICAL USE

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In the course of experiments on gas gangrene,[9] 7 guinea pigs which had been infected with *Cl. perfringens* and treated subcutaneously with penicillin died, although they had shown no symptoms of gas gangrene. They had received 2600 to 4000 Florey units (F.U.) per kg. per day in 7 doses daily for 3 to 4 days. Deaths occurred 12 to 72 hours after treatment had been stopped. The only signs of illness were extreme anorexia, ruffled fur, lethargy and loss of weight. At autopsy, no local or systemic evidences of gas gangrene were found, and no anaërobes were recovered in cultures, nor were there any findings suggesting death might be due to any spontaneous intercurrent infection. The amounts of penicillin given to these animals were well below the toxic level for other animals, but the possibility remained that guinea pigs are more susceptible to penicillin than other animals. To investigate this possibility, further experiments were undertaken.

Experiments. Penicillin used in these experiments was prepared from crude culture filtrates of *Pencillium notatum* grown on Czapek-Dox medium[3] modified by substitution of brown sugar for glucose.[7] Preparations Pooled Lot (100 F.U. per mg.) and Lot No. 27404 (90 F.U. per mg.) were sodium salts for clinical use prepared by Dr. J. C. Hoogerheide and Mr. C. W. Eberlein by extraction of the culture filtrate at pH 6.5 with butanol, replacement of the latter by benzene, the reëxtraction with bicarbonate followed by transfer, via ether, into phosphate buffer and finally into bicarbonate solution.* These preparations were actually used clinically. Preparation M591 (400 F.U. per mg.) was prepared by one of us (H.B.M.) from a product assaying 150 F.U. per mg. by a purification procedure involving selective reëxtraction from ether solution with pH 5 buffer, conversion into the sodium salt, precipitation of impurities with silver sulfate and preparation of the sodium salt from the material remaining in the supernatant solution. Preparation A872 (250 F.U. per mg.) prepared by Dr. A. E. O. Menzel, originated from a pool of preparations which had been purified by transferring into chloroform in the presence of ammonium sulfate at pH 4, extracting with buffer at pH 6, repeating the chloroform procedure and extracting with buffer at pH 5.5. The acidified buffer solution was transferred to ether and the sodium salt prepared by extraction with sodium bicarbonate.* Sodium salt M868 was prepared by

* We wish to express our thanks to Mr. C. W. Eberlein and Dr. J. C. Hoogerheide of the Biological Laboratories, E. R. Squibb & Sons, and to Dr. A. E. O. Menzel of the Division of Microbiology, The Squibb Institute for Medical Research, for supplying these materials.

H. B. M. by the amyl acetate extraction procedure from a batch of deep culture filtrate. Further purification was effected by chromatographic methods.*

The activity of these preparations was determined by *in vitro* titration against a 6-hour culture of *Staphylococcus aureus* strain H.† Decreasing amounts of penicillin were placed in a series of 13 × 100 mm. tubes, the volume in each tube brought up to 1 ml. with broth and 1 ml. of a 10^{-6} dilution of the culture in broth added to each tube. The tubes were shaken and incubated at 37° C. for 16 hours. The smallest amount of penicillin inhibiting growth as indicated by lack of any turbidity after shaking the incubated tubes was taken as the end-point and the number of Florey units per milligram determined by comparison with a standard preparation of penicillin simultaneously tested in the same way. The standard had been previously assayed by comparison with a standard preparation of known potency.‡[2] All penicillin was kept either dry or in aqueous solution at 1 to 3° C. under which conditions it was stable for the periods under observation. Both for intravenous and for subcutaneous injection the penicillin was prepared in distilled water.

Acute Toxicity of Penicillin. The comparative toxicity of penicillin given intravenously in a single injection to mice, guinea pigs and rabbits is presented in Table 1. All of the animals received the same preparation (Lot No. 27404) containing 90 F.U. per mg. The solutions contained no particles and were injected slowly to avoid reactions due to hypertonicity.

TABLE 1.—ACUTE TOXICITY OF PENICILLIN GIVEN INTRAVENOUSLY TO MICE, GUINEA PIGS AND RABBITS

(Penicillin Lot No. 27404 Containing 90 F.U. mg.)

Animals	Wt. (gm.)	Dose F.U.	F.U./kg.	Mg./kg.	Result
10 mice	20	1,395	69,700	774	No reaction
5 mice	20	1,800	90,000	1000	4 died in 4 hrs. 1 died in 5 days
1 mouse	20	2,511	125,000	1388	Sick, recovered
4 mice	20	2,790	139,000	1544	1 died in 30 min. 2 died in 16 hrs. 1 sick, recovered
Guinea pig:					
No. 179	225	4,185	18,000	200	No reaction
No. 180	211	5,580	27,900	310	No reaction
No. 181	178	5,580	31,300	347	No reaction
No. 185	230	12,370	53,000	588	Died in 93 hrs.
No. 186	214	12,370	57,000	633	Sick, killed in 9 days
No. 184	219	15,462	75,000	833	Sick, killed in 9 days
No. 183	217	15,462	75,000	833	Died in 2 min.
No. 182	305	30,925	101,000	1122	Died in 10 min.
Rabbit:					
No. 3	790	37,110	47,000	533	No reaction
No. 2*	770	55,665	70,200	780	Died in 72 hrs.
No. 1	1100	122,310	111,000	1233	Died in 1 hr.

* Coccidiosis possible cause of death.

The numbers of animals were too small to determine accurately the minimal fatal dose, and could not be increased because of lack of material. However, it is apparent from these experiments that, although the guinea pigs appear slightly more sensitive, there is no great difference in the susceptibility of mice, guinea pigs and rabbits to a single intravenous dose of penicillin. Also it is obvious that the acute toxicity

* Details of the purification procedures will be published in connection with chemical studies on penicillin which are in progress in the Division of Organic Chemistry of The Squibb Institute for Medical Research (Drs. Oskar Wintersteiner, Harold B. MacPhillamy and Arthur E. O. Menzel).

† We are indebted to Dr. N. G. Heatley for this strain of *Staphylococcus aureus*.

‡ This standard was obtained through the courtesy of Dr. H. W. Florey.

of penicillin is not very great. This is borne out by the reports of other workers. Chain, Florey, Gardner, Heatley, Jennings, Orr-Ewing and Sanders[2] found that 10 mg. intravenously had no effect on mice and rats, and that 40 mg. had no effect on the blood pressure, heart beat or respiration of a cat. They did not give the activity of their penicillin in Florey or any other units. Hobby, Meyer, and Chaffee[8] gave 32 mg. (1.8 gm. per kg.) as the L.D. 50 for 18 gm. mice, and reported no reaction in guinea pigs following the injection of 320 mg. (1.3 gm. per kg.), but they also did not give the potency of their penicillin or the number of animals used. Abraham, Chain, Fletcher, Florey, Gardner, Heatley and Jennings[1] were able to produce a severe reaction in mice by the injection of 20 mg. of a preparation containing 40 to 50 F.U. per mg., but Florey and Jennings[5] reported that 20 mg. of penicillin containing 250 to 325 F.U. per mg. could be given to 20 gm. mice without ill effects. This indicates that purification reduces the acute toxicity of penicillin. The results of the experiments reported here, in which only one penicillin preparation (90 F.U. per mg.) was used and a dose of 1 gm. per kg. produced severe reactions and death in mice and rabbits, are in agreement with those of Robinson[11] who produced 90% mortality with the intravenous injection of mice with 90,000 F.U. per kg. of a preparation containing 60 F.U. per mg., but with a preparation containing 400 F.U. per mg., deaths did not occur when the intravenous dose was below 600,000 F.U. per kg. In an experiment using small numbers of mice we obtained only slight reactions with 250,000 F.U. per kg. of a preparation containing 500 F.U. per mg.,[10] further indication that purification lowers the toxicity.

Toxicity of Multiple Subcutaneous Doses of Pencillin. In the experiments on treatment of gas gangrene with penicillin, the guinea pigs had received multiple doses subcutaneously. Therefore, the next experiment was designed to compare the reactions of guinea pigs, mice and rabbits to repeated subcutaneous injections of penicillin. Two guinea pigs and one rabbit received about the same dose per kg. of body weight and 6 mice about one-half this dose per kg. of the same penicillin preparation. The results are given in Table 2.

TABLE 2.—TOXICITY OF REPEATED SUBCUTANEOUS DOSES OF PENICILLIN FOR GUINEA PIGS, MICE AND RABBITS

(Penicillin Preparations Pooled Lot, 100 F.U./mg., Given 7 Times Daily)

Animal	Wt. (gm.)	Single dose F.U.	Penicillin per kg. per day	Total amount given	Result
Guinea pig:					
No. 149	278	500	12,500 F.U. 125 mg.	8,000 F.U. 80 mg.	Moribund; killed 2d day
No. 150	283	500	12,500 F.U. 125 mg.	11,000 F.U. 110 mg.	Moribund; killed 3d day
Rabbit:					
No. 37	860	1500	12,500 F.U. 125 mg.	33,000 F.U. 330 mg.	No reaction after 4 days treatment
Mice:					
Nos. 1 to 6	20	22.8	7,780 F.U. 77 mg.	501 F.U. 5 mg.	No reaction after 4 days treatment

Both guinea pigs receiving the pooled lot of penicillin lost weight and, when moribund, were killed to obtain fresh material for sections. The mice and rabbit remained normal throughout the experiment.

These results indicated that guinea pigs are more susceptible to continued subcutaneous injections of penicillin than mice and rabbits. However, since the penicillin available was relatively impure, it was possible that contaminating substances present were more toxic for the guinea pig than for the rabbit or the mouse.

In an attempt to determine whether further purification by different methods would alter the toxicity of penicillin for guinea pigs, 3 preparations of high potency were given subcutaneously over a period of several days. The amounts of preparations M591 (400 F.U. per mg.) and A872 (250 F.U. per mg.) were sufficient for only one animal on each preparation, and were given in 7 doses daily. Preparation M868 (1068 F.U. per mg.) was given 3 times daily. The experiment is summarized in Table 3.

TABLE 3.—TOXICITY FOR GUINEA PIGS OF REPEATED SUBCUTANEOUS DOSES OF MORE HIGHLY PURIFIED PENICILLIN

Animal	Wt. (gm.)	Penicillin preparation	Single dose F.U.	Penicillin per kg. per day	Total dose given	Result
No. 163	269	M591 400 F.U./mg.	400 changed to 200 on 3d day	11,500 F.U. 26 mg. 5,600 F.U.	7,000 F.U. 17 mg.	Moribund; killed on 4th day
No. 164	250	A872 250 F.U./mg.	500 changed to 250 on 3d day	14,000 F.U. 56 mg. 7,000 F.U.	8,750 F.U. 35 mg.	Died on 4th day
No. 295	240	M868 1068 F.U./mg.	550	7,000 F.U. 6.5 mg.	11,000 F.U. 10.3 mg.	Sick 3d and 4th day; recovered; marked local irritation
No. 296	330	"	750	7,000 F.U. 6.5 mg.	7,050 F.U. 6.6 mg.	Died on 4th day
No. 297	355	"	800	7,000 F.U. 6.5 mg.	14,400 F.U. 13.4 mg.	Died on 7th day
No. 298	310	"	700	7,000 F.U. 6.5 mg.	14,000 F.U. 13.1 mg.	Sick 3d and 4th days; recovered; marked local irritation
No. 299	265	"	850	7,000 F.U. 6.5 mg.	10,200 F.U. 9.5 mg.	Moribund; killed on 4th day

Only the higher potency material (M868) showed any decrease in toxicity. Two out of 5 guinea pigs given this preparation became sick on the 3d day, but by the 6th day were improving and ultimately survived. Because of the small number of animals used, these results may be due to chance alone, but it is also possible that this does indicate a decrease in toxicity with increased purification. Further experiments with highly purified material will be necessary to decide this point. The fact remains that even with a 10-fold increase in purity, penicillin was still toxic for guinea pigs.

For further comparative data on guinea pigs, mice and rabbits, a more extensive experiment was carried out in which different doses of penicillin were given subcutaneously over a period of several days. Some of these animals were those which had survived a single dose intravenously. Subcutaneous injections were begun 24 hours after the intravenous dose. In an attempt to produce toxic reactions in mice and rabbits similar to those seen in guinea pigs, 2 rabbits (Nos. 3, 4) and 6 mice were given doses 5 to 7 times greater per kilogram than the dose which produced toxic reactions in guinea pigs. All animals received the same preparation of penicillin (Table 4).

TABLE 4.—TOXICITY OF REPEATED SUBCUTANEOUS DOSES OF PENICILLIN FOR GUINEA PIGS, MICE AND RABBITS

(Penicillin Lot No. 27404 Containing 90 F.U./mg., Given 3 Times Daily)

Animal	Wt. (gm.)	Single dose F.U.	F.U. per kg. per day	Total amount given F.U.	Result
Guinea pig:					
No. 179*	215	500	7,000	6,500	Died 5th day
No. 180*	194	500	7,700	2,000	Died 2d day
No. 181*	174	500	8,600	4,000	Died 3d day
12 mice*	20	100	15,000	2,500	No reaction after 8 days treatment; killed on 9th day
6 mice	16	220	41,250	6,160	No reaction after 9 days treatment; killed on 9th day
Rabbit:					
No. 3*	780	12,220 changed to 3,375 on 4th day	47,000 15,000	143,855	No reaction after 7 days treatment; killed on 9th day
No. 4	710	14,200 changed to 3,375 on 4th day	60,000 16,000	200,000	No reaction after 7 days treatment; killed on 9th day

* See Table 1 for previous treatment of these animals. SC doses were begun 24 hours after IV dose

The mice showed no reaction, the guinea pigs lost weight and died, and the rabbits lost weight during the first part of the treatment period, but regained this loss during the latter part. This regain in weight was probably due to the reduction in dose of penicillin necessitated by lack of material. However, extreme caution is necessary in evaluation of loss of weight in relation to toxicity because of the possible rôle of chronic pneumonia or coccidiosis which occur all too frequently among normal guinea pigs and rabbits.

To exclude the possibility that toxicity is a property only of the penicillin prepared at New Brunswick, a sample of penicillin from another source* was tested in guinea pigs. Treatment and results are given in Table 5.

TABLE 5.—TOXICITY OF REPEATED SUBCUTANEOUS DOSES OF MERCK PENICILLIN FOR GUINEA PIGS

(Preparation Containing 150 F.U./mg., Given 3 Times Daily)

Guinea pig	Wt. (gm.)	Dose F.U.	F.U. per kg. per day	Total amount given F.U.	Result
No. 187	213	500	7040	5000	Died on 4th day
No. 188	207	500	7200	7500	Died on 5th day
No. 189	218	500	6880	7500	Died on 5th day
No. 190	290	696	7200	8352	Sick; killed on 4th day
No. 191	273	655	7200	7860	Died on 4th day

Since 4 out of 5 of the animals died and the other was sick when killed, it was concluded that the toxic property of penicillin is not confined to our preparations.

Guinea pigs are unique among the common laboratory animals for their inability to synthesize vitamin C. This fact and the results of our experiments on toxicity of repeated doses of penicillin for guinea pigs suggested that there might be some connection between the metabolism of vitamin C and penicillin toxicity. All guinea pigs were

* We are indebted to Dr. Randolph T. Major of Merck & Co., Rahway, N. J., for the sample of penicillin. Its method of preparation was, in brief, as follows: extraction by an amyl acetate procedure of a crude culture filtrate from a brown-sugar Czapek-Dox type medium.

fed a balanced diet with liberal amounts of greens, and no gross evidence of scurvy was ever found in those dying of penicillin toxicity. However, in view of the reports that certain organic compounds caused an increase in the excretion of vitamin C in the rat and that administration of large amounts of vitamin C had a detoxifying action on benzene, lead and arsenic compounds, and on some of the bacterial toxins (see Rosenberg's monograph[12] and the review of Györgi[6]) it was decided to investigate the rôle of vitamin C in penicillin toxicity in guinea pigs.*

In one experiment, a group of 4 guinea pigs on a vitamin C deficient diet[4] was given 10 mg. of sodium ascorbate subcutaneously daily for 3 days before penicillin treatment, but none during such treatment. Another group of 4 on a vitamin C deficient diet were given 10 mg. of sodium ascorbate subcutaneously daily for 3 days prior to and during penicillin treatment, and a third group on regular diet with a liberal amount of greens were given no sodium ascorbate. Seven thousand F.U. of penicillin (134 F.U. per mg.) per kg. per day were given subcutaneously in 3 doses daily. At the time of death pieces of liver and the adrenals were weighed and placed in 5% metaphosphoric acid for determinations of ascorbic acid. The results are shown in Table 6.

TABLE 6.—THE EFFECT OF VITAMIN C ON THE TOXICITY FOR GUINEA PIGS OF REPEATED SUBCUTANEOUS DOSES OF PENICILLIN

(7000 F.U./kg. per Day of Penicillin M869 [134 F.U./mg.], Given 3 Times Daily)

Guinea pig	Wt.	Vitamin C treatment	Time of death after penicillin treatment began (day)	Ascorbic acid content	
				Liver (mg./gm.)	Adrenals (mg./gm.)
No. 300	203	10 mg. sodium ascorbate SC	2d	0.061	0.23
No. 301	237	daily for 3 days before peni-	7th		
No. 302	284	cillin treatment; no further	8th		
No. 303	270	vitamin C	5th		
No. 304	245	10 mg. sodium ascorbate SC	3d		
No. 305	239	daily for 3 days prior to and	8th		
No. 306	237	during penicillin treatment	12th		
No. 307	234		3d	0.15	0.47
No. 308	247	No sodium ascorbate; greens	Survived		
No. 309	272	included in diet	6th		
No. 310	224		3d	0.037	0.083
No. 311	267		6th		
No. 312	226	100 mg. sodium ascorbate for	3d		
No. 313	253	3 days prior to and during	4th	0.48	0.84
No. 314	234	penicillin treatment*	3d		
No. 315	230	No sodium ascorbate; greens	4th		
No. 316	303	included in diet*	2d		
No. 317			6th		

* On the 2d day of penicillin treatment preparation 29114, containing 99 F.U./mg., replaced preparation M869.

Although 10 mg. of sodium ascorbate a day was about 5 times the dose necessary to prevent scurvy and raised the ascorbic acid content of the liver and adrenals about 5 times over that of guinea pigs fed the regular laboratory diet, it did not protect the guinea pigs from the toxic action of the penicillin.

In another experiment, 3 guinea pigs on a vitamin C deficient diet were given 100 mg. of sodium ascorbate daily for 3 days prior to and

* We are indebted to Dr. Laslo Kajdi of the Department of Pediatrics, The Johns Hopkins Hospital, Baltimore, for suggesting that vitamin C might be connected with penicillin toxicity in guinea pigs and for the assays of ascorbic acid.

during penicillin treatment, and 3 guinea pigs on regular diet with greens were given no sodium ascorbate. Penicillin was given in the usual way (7000 F.U. per kg. per day). Two preparations were used, one containing 134 F.U. per mg., the other, 99 F.U. per mg. At the time of death, liver and adrenals were taken for ascorbic acid assay (Table 6) and sections were made of the costochondral junctions, the head of the tibia, and the lower jaw for detection of sub-clinical scurvy. Study of these microscopic preparations revealed no abnormalities.

Since all but one of the guinea pigs in both experiments died, in spite of the massive doses of vitamin C, it was concluded that vitamin C does not have a protective action on penicillin toxicity.

Pathologic Findings. Since the lesions found in each species of animals, regardless of dose of penicillin given, were approximately the same, the pathologic findings will be discussed together.

GUINEA PIGS. No lesions were seen in the gross or microscopically in the central nervous system, lung (with the exception noted below), spleen, lymph nodes, intestine, pancreas, kidney, adrenal, gonads or voluntary muscle except when the latter was subjacent to the site of inoculation.

Heart. In 12 instances, this organ was normal, but in 3 (G.P. 180, 181 and 299) there were lesions in the wall of the left ventricle consisting of necrosis of several muscle fibers and surrounding infiltration with monocytes and a few polymorphonuclear cells.

Site of Inoculation. In the gross, the area was edematous and yellowred in color when compared to normal subcutaneous tissue.

Microscopically the picture was one of edema of the subcutaneous tissue and infiltration, of greater or lesser degree, of this tissue with monocytes and some polymonuclear leukocytes (Fig. 3). In the majority of cases the damage extended into the subjacent voluntary muscles. Muscle fibers in varying degrees of destruction and phagocytosis were seen and there was considerable infiltration of cells of the same type as seen in the subcutaneous tissue.

In 1 case penicillin was accidentally administered into the lung by the trachea. A widespread acute pneumonic consolidation and fibrinous pleurisy resulted.

Liver. Foci of necrosis, often of considerable size, were present in many of the guinea pigs given penicillin. However, although liver damage was frequently observed, its importance in these animals seemed questionable and an exhaustive search was made for similar lesions in apparently normal animals. Six guinea pigs from each of the two sources from which the experimental animals were obtained, were killed and 6 pieces of liver taken from each animal. Foci of necrosis were present in 2 out of the 6 animals in one group and in 3 of the 6 in the other group. In addition scars suggesting healed foci were found in 1 animal in each group.

RABBITS. No lesions were found in the central nervous system, lung, spleen, lymph nodes, pancreas, liver, kidney, adrenal, gonads, heart, or voluntary muscle.

Site of Inoculation. In the gross, the subcutaneous tissue was greatly thickened by edema and blood-tinged in color. Microscopically, the picture resembled that described for the guinea pigs, except in degree.

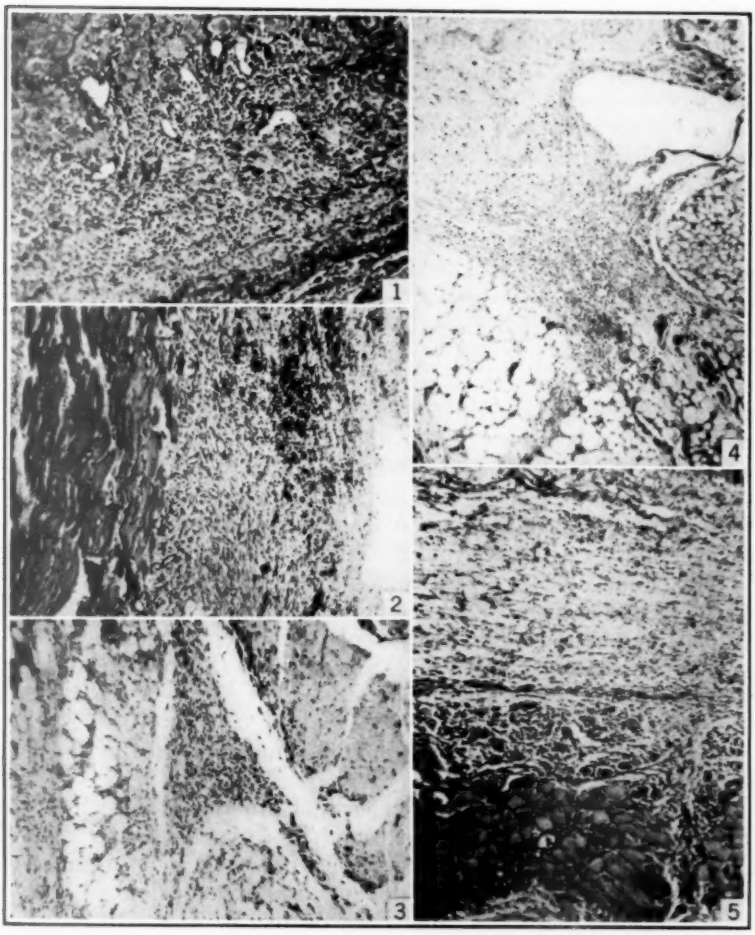

FIG. 1.—Site of inoculation, rabbit No. 3, showing cell infiltration and destruction of muscle fibers. (× 100 hematoxylin and eosin.)

FIG. 2.—Site of inoculation, guinea pig No. 229, showing cell infiltration, destruction of muscle fibers and early fibrosis. (× 100 hematoxylin and eosin.)

FIG. 3.—Site of inoculation, guinea pig No. 164, showing cell infiltration. (× 100 hematoxylin and eosin.)

FIG. 4.—Site of inoculation, mouse, showing cell infiltration and edema. (× 100 hematoxylin and eosin.)

FIG. 5.—Site of inoculation, guinea pig No. 227, showing cell infiltration, edema and destruction of muscle fibers. (× 100 hematoxylin and eosin.)

In the rabbits examined, the process was very intense. Hemorrhage was added to edema in the subcutaneous tissue, polymorphonuclear cells were more numerous than in the guinea pig and the destruction of

subjacent voluntary muscle fibers was considerably more extensive (Fig. 1).

MICE. No lesions were found in the gross or microscopically in the central nervous system, lung, spleen, liver, lymph nodes, intestine, pancreas, kidney, adrenal, gonads, heart or voluntary muscle.

Site of Inoculation. In the gross the subcutaneous tissue was very edematous but only slightly blood-tinged. Microscopically, there was considerable edema of the subcutaneous tissue. While the cell infiltration was of the same type as that noted in the guinea pigs and rabbits, it was less in degree in all mice examined (Fig. 4). Destruction of the voluntary muscle fibers and surrounding cell infiltration was about the same as in the guinea pigs.

In the foregoing experiments evidence has been presented that the penicillin preparations used in this investigation were toxic for guinea pigs. However, the doses given to demonstrate this toxicity have been larger, in every case, than those given to man in present clinical studies. Therefore, 3 guinea pigs (227, 228, 229) were given 1000 F.U. per kg. per day (approximately the dose given to man) in 3 subcutaneous doses daily for 20 days. During this time their weights varied, but the general trend was toward gain rather than loss. They exhibited no signs of illness except subcutaneous edema at the site of injection. On the 21st day, all pigs were killed and sections taken for study.

All inoculations had been made in the same general area, and therefore, as might be expected from the results outlined above, at autopsy the site of inoculation presented a picture of intense inflammation, both acute and chronic. Edema and fresh and older hemorrhages were frequent. There was infiltration of polymorphonuclear leukocytes and some monocytes and destruction of muscle fibers (Fig. 5). In addition, there were large numbers of fibroblasts and some fibrocytes and newly formed capillaries (Fig. 2).

In the liver of 1 out of the 3 animals, numerous foci of the type discussed above were found.

Discussion. In the literature, reports of experiments in which animals have been given a single intravenous dose of penicillin have shown that its acute toxicity is very low. Since penicillin is not a pure substance and preparations vary in potency, the exact toxic dose has not been established. Obviously the assay of toxicity should be based on Florey units as well as milligrams of substance given. For white mice, we found the lethal intravenous dose to be about 90,000 F.U. (1 gm.) per kg. using a preparation containing 90 F.U. per mg., but in another experiment[10] using more highly purified material (500 F.U. per mg.) 250,000 F.U. per kg. caused only a slight reaction. Abraham, Chain, Fletcher, Florey, Gardner, Heatley and Jennings[1] reported the toxic dose as about 50,000 F.U. (1 gm.) per kg., but when more highly purified preparations were used, Florey and Jennings[3] gave mice 375,000 F.U. (1 gm.) per kg. intravenously, without ill effects, and Robinson[11] found that doses of 600,000 F.U. per kg., or below, were not lethal when given intravenously to mice. These results indicate that purification removes some of the substances responsible for this acute toxicity.

Very little data have been given on toxicity for other animals.[1,2,8] In our experiments 111,000 F.U. (1.2 gm.) per kg. was a lethal dose for rabbits and 75,000 F.U. (0.8 gm.) per kg. killed guinea pigs when given intravenously. In experiments reported in the literature usually no mention is made of the numbers of animals used, and in our experiments only small numbers were given any one dose because of lack of sufficient material for large scale experiments.

When penicillin was given subcutaneously over a period of several days or weeks to mice, rabbits and guinea pigs, the picture was altered. All animals showed a severe reaction at the site of injection. Edema of the subcutaneous tissue, infiltration of monocytes and polymorphonuclear leukocytes, and destruction of subjacent voluntary muscle were found in all animals, and in the rabbits and 3 of the guinea pigs there were hemorrhages. Other than this, the mice and rabbits tolerated the penicillin injections well. These results are in agreement with those of Robinson[11] who found that doses below 192,000 F.U. per kg. per day given in several subcutaneous injections daily for 5 days to mice were not toxic. In the guinea pigs, however, prolonged subcutaneous injections of penicillin prepared at different places and by different methods caused death.

Until penicillin is prepared in a chemically pure state, it will not be possible to determine whether or not contaminating substances are responsible for all of the toxicity of penicillin preparations. None of the preparations tested in these experiments were non-toxic, even a preparation having a 10-fold increase in purity was still toxic although it failed to kill all of the guinea pigs injected. It is possible that further purification will remove all of the toxic substances. However, it should be stressed that the penicillin preparations used were all as pure as, and in many cases purer than those at present in use in human treatment, and some were actually used in such treatment.

The fact that present preparations are toxic for guinea pigs when given subcutaneously does not mean that penicillin is toxic for man. When treated with the same dose of penicillin per kg. as that given to man, guinea pigs did not die and, in fact, failed to show any signs of toxicity. However, it is suggested that chronic toxicity for man be borne in mind and that care be taken to administer penicillin in several widely separated places when given subcutaneously or intramuscularly.*

Summary. 1. The acute toxicity of penicillin for mice, guinea pigs and rabbits was low; about 100,000 F.U. (1 gm.) per kg., given intravenously, caused a severe reaction and death.

2. Seven thousand to 12,000 F.U. per kg. per day of penicillin, as prepared for clinical use, given subcutaneously over a period of several days caused death of guinea pigs, but not of mice or rabbits. However,

* In his experience with the clinical use of penicillin Dr. Chester S. Keefer has found that, when given intramuscularly, penicillin dissolved in salt solution does not cause any local signs of irritation or any discomfort. When given subcutaneously and dissolved in distilled water rather than salt solution, penicillin may produce some local irritating effect, although this has not been severe enough to raise any problem. (Personal communication.)

a dose approximately that used clinically (1000 F.U. per kg.) given subcutaneously for 20 days did not kill guinea pigs.

3. All animals given penicillin subcutaneously showed a severe reaction at the site of injection.

4. Seven samples of penicillin prepared by different methods in two different places were toxic when given subcutaneously to guinea pigs for several days.

5. Large doses of sodium ascorbate did not protect guinea pigs from the toxicity of repeated subcutaneous doses of penicillin.

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DISSEMINATED NECROTIZING VASCULARITIS—THE TOXIC ORIGIN OF PERIARTERITIS NODOSA

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Since Rokitansky[21] first described arterial aneurysms in 1852, the literature has become voluminous in regard to certain vascular problems. Kussmaul and Maier[13] in 1866 contributed a classical description of the pathology which they had noted in a patient with widespread vascular disease. Following the publication of this thesis the problem of vascularitis, commonly termed periarteritis nodosa, remained a closed chapter in medical annals for many years. During the present century frequent case reports with autopsies have been contributed, notably those by Klotz,[12] Middleton,[17] Friedberg,[5] Harbitz,[9] Bennett and Levine,[3] Longcope,[16] Wordley,[26] Taylor and Farley,[23] Haining and Kimball,[8] Harris,[10] Leishman,[15] and Osler.[19]

Spiegel[22] states that approximately 12% of her patients were diagnosed by clinical study during life. The purpose of this communication is to make a brief report of 10 patients, diagnosed antemortem as disseminated vascularitis, confirmed at the postmortem table, and

subsequently by microscopic study. Contrary to recently expressed opinions we have been unable to correlate these vascular lesions with preceding sulfonamide therapy.

Etiology. On reviewing the literature one is impressed with the frequency with which allergy has been alluded to as a causative factor in disseminated vascular disease. Clark and Kaplan[4] have reported 2 patients who died following intravenous antipneumococcus serum. They found widespread vascular lesions which they thought were suggestive of periarteritis nodosa. Rich[20] recently demonstrated a small group of patients whose lesions were those of widespread vascularitis which occurred subsequent to the ingestion of one of the sulfonamides, or followed administration of serum. He implied that the arterial lesions were due to an "anaphylactic type of hypersensitive reaction" and has produced similar lesions in experimental animals.

Considerable attention has been given to the possible relationship of this disease to rheumatic fever. Ophuls[18] in 1923 felt that his patients had had subacute rheumatic manifestations as a prelude to their vascular problem. Friedberg and Gross,[5] and Spiegel[22] reported a group that showed Aschoff bodies in the myocardium. However, Von Glahn and Pappenheimer[24] showed in their studies of rheumatic arteritis that the lesions were distinctly different from those seen in periarteritis nodosa. We have been unable to demonstrate Aschoff bodies in a single patient. On the other hand there were 2 instances showing involvement of the mitral or tricuspid leaflets. An infectious etiology of the disease has many adherents, notably Klotz[12] and Lamb.[14] Arkin[1] believes that the disease is a definite clinical entity probably due to a virus, but no definite virus studies have been made. We have been unable to demonstrate any infectious agent in the blood, or in the vessel walls. Gruber[6] believed that the arterial lesions were due to a peculiar hyperergic reaction resulting from a variety of infectious agents. Generalized inflammation with local necrosis has been described involving the small arteries as a residue of diphtheria, influenza, scarlet fever, typhus fever, and a variety of chronic suppurative diseases.

Visceral Lesions. The visceral lesions of vascularitis lend themselves to a ready description and classification under the microscope, but clinically diagnostic errors may be made, due to the puzzling combinations of symptoms which may present. Hematuria may suggest renal neoplasm. Abdominal complaints may lead to exploratory laparotomy. Chest symptoms are identical to those associated with pneumonia or pulmonary infarction. A better comprehension of disseminated vascularitis is obtained when a brief synthesis of these visceral lesions is made in the light of their pathologic similitude.

The Kidney. Impairment of renal functioning tissue was the most constant feature of this syndrome. All of our patients revealed widespread kidney lesions. This is comparable to Arkin's[1] group which showed an incidence of 80% renal involvement. Gruber[6] has classified these lesions as active and passive. The active lesions are the earlier ones, being initiated possibly by a hyperergic reaction on the part of

the renal vessels. The later lesions include aneurysm, infarction, and tubular atrophy. (Fig. 1.) In our group there was no apparent correlation between the extent of the kidney lesion and the degree of nitrogen retention. The character of the hypertension was not unusual except that it was a terminal affair with 3 of these patients.

The Liver and Gall Bladder. There was hepatic involvement in every case. Jaundice was not evident in a single instance. There were small areas of infarction with necrosis and subcapsular hemorrhage, as well as hepatic and cholecystic thromboses with marked lymphocytic and plasma cell infiltration. Cirrhosis of the liver was not demonstrable.

The Pancreas. In all patients the pancreatic vessels showed lymphocytic and plasma cell infiltration with intimal thickening of the small vessels, accompanied by infarctions.

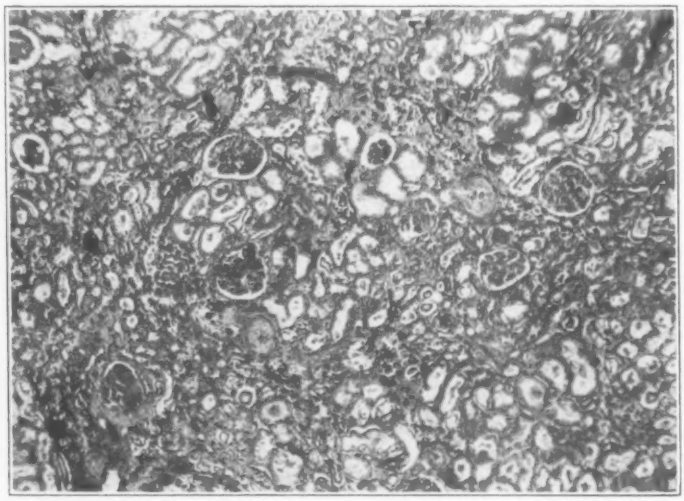

FIG. 1.—Thrombosis of several renal vessels is shown with early necrosis of their walls (H and E stain.) × 100.

The Spleen. Splenic vessels were involved in every patient with moderate intimal and medial proliferation of the smaller vessels. (Fig. 2.) There were multiple thromboses, infarction with necrosis, and hemorrhage. The sinusoids were distended and a moderate amount of brown pigment was seen within large mononuclear cells.

The Adrenal. Strangely enough we were able to demonstrate definite vascularitis in only one of the adrenal specimens. (Fig. 3.) This section showed one small artery surrounded by a thick cuff of polymorphonuclear cells, monocytes, plasma cells, and lymphocytes. There was early necrosis about the vessel as indicated by poor staining quality and fragmentation of the leukocytes. There was intimal proliferation with almost complete occlusion of the lumen of the vessel.

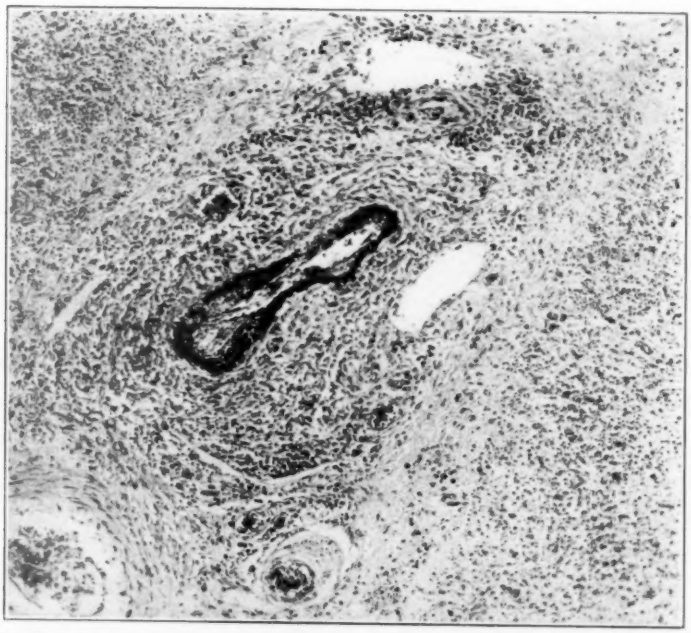

FIG. 2.—The splenic vessels show moderate intimal and medial proliferation with partial thrombosis. (H and E stain.) × 100.

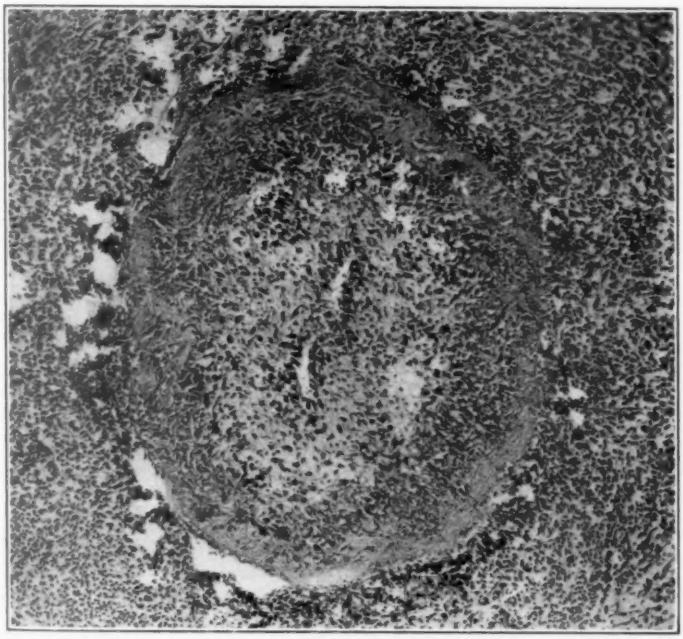

FIG. 3.—This section is from an adrenal vessel. There is some fibrinoid change. The vessel wall reveals many plasma cells, polys, and a few lymphocytes. (H and E stain.) × 100.

The Gastro-intestinal Tract. Small nodules were demonstrable in the mesentery of the small bowel following the course of the mesenteric

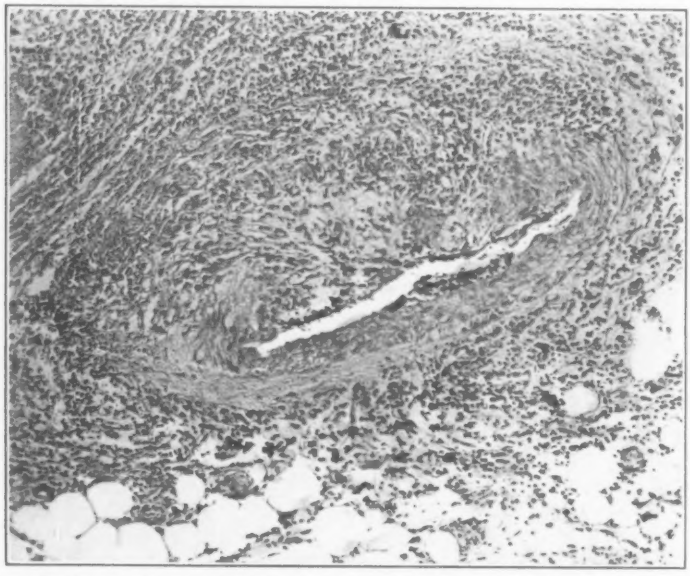

FIG. 4.—This vessel from the tricuspid valve shows cellular infiltration beneath the intima by large mononuclear cells, plasma cells, and polys. (Giemsa stain.) × 100.

FIG. 5.—Section from the right anterior descending branch of the coronary artery shows a thick perivascular cuff of polymorphonuclear cells, monocytes, plasma cells and lymphocytes. There is marked edema of the vessel wall with a narrowing of its lumen. (H and E stain.) × 100.

veins and arteries. The appendix of 1 patient showed a localized abscess with gangrene, due to thrombosis of the appendiceal artery. Obliterative arteritis involved many of the smaller intestinal vessels, and the main gastric artery was largely occluded in 1 instance.

Cardiovascular Lesions. Involvement of the myocardium and the endocardium was frequently demonstrable. One section of a heart taken through the tricuspid valve revealed the presence of a diffuse process. (Fig. 4.) There was an area of necrosis beneath the endocardium almost perforating it in many places. These areas of necrosis were characterized by great numbers of polymorphonuclear cells, some plasma cells, and a few monocytes. The eosinophil was not prominent. The endocardial surface of the ventricle and auricle was rarely involved. One coronary artery was almost completely occluded by thrombus formation (Fig. 5). The artery wall was edematous, thickened, and

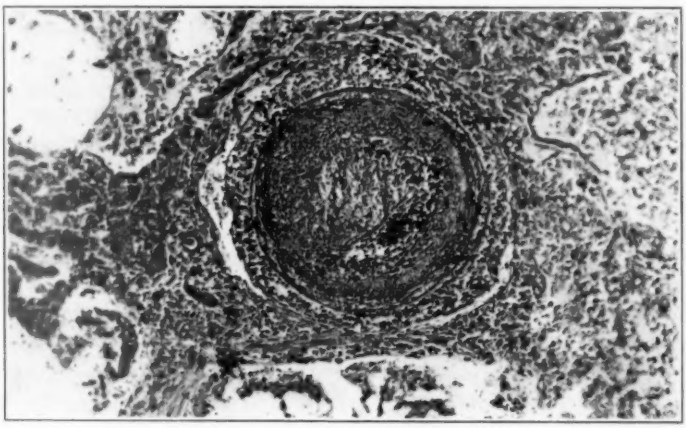

FIG. 6.—This vessel from the lung shows complete thrombosis of the vessel with early necrosis. (H and E stain.) × 100.

infiltrated by monocytes and polymorphonuclear cells. There was marked intimal hyperplasia. The muscle bundles were widely separated in a few sections with a diffuse infiltration of monocytes and plasma cells. Aschoff formation was not noted in any of these sections.

The Lung. The lung sections showed marked congestion, and the vessel walls were slightly thickened. Numerous bronchi were filled with fibrin, erythrocytes and some polymorphonuclear cells. The bronchial walls were frequently infiltrated with these cells giving evidence of bronchopneumonia (Fig. 6).

Discussion. It seems perfectly clear that the pathologic lesions herein described show marked similarity, so much so that we believe these arterial lesions point to a disease of the blood-vessels, due either to a specific bacterial agent, or a specific vascular reaction to some unidentified toxin or other harmful mechanism.

That the sulfonamides might produce these vascular lesions is

implied by Rich[20] as all of his patients had been given sulfonamide, antipneumococcus serum, or both. The lesions demonstrated so well by our sections are largely old, and it is untenable that the pathology could have developed during the acute terminal illness. Furthermore, only 4 of these patients had received sulfonamide therapy during the course of or preceding their terminal illness.

In searching for some common etiologic denominator we sought for a history of serum sickness, urticaria, and asthma. None of these conditions had played a part in the previous history of a single patient. Five had had frequent upper respiratory infections. Two soldiers had a history of rheumatic fever in early childhood. We do not know just what part these earlier infections played in the causation of this disease. The uniformity of the arterial damage has suggested a specific bacterial agent or specific vascular reaction to this agent. This idea has many early adherents, including Klotz,[12] Lamb[14] and Longcope.[16] Harris and Friedrichs[11] and Von Hann[25] were able to produce similar arterial lesions by injecting rabbits with bacterial products but these reports of experimental reproduction of the disease have not been universally accepted. Streptococci have occasionally been identified after direct culture of the arterial lesions, but our postmortem cultures of the vessels have proven to be sterile. The rich lymphatic system of the mediastinal vessels and those of the celiac axis should readily permit the entrance of infectious agents. It is thought that the bacteria enter the vessel walls through the vasa vasorum. This is demonstrated by the focal inflammatory reaction so often found in the myocardium during the course of acute rheumatic fever. This involvement of the lymphatic channels and nutrient vessels would readily damage the invaded organ.

Gruber[7] contended that periarteritis nodosa is due to a specific reaction occurring in previously sensitized vessels following the wake of a variety of infectious agents. The sensitizing infection need not be a severe one, but it may follow rheumatic fever, typhus fever, gonorrhea, furunculosis, and a variety of purulent infections. Since no bacteria were found after culture of these vascular lesions we believe that these widespread visceral lesions have a non-specific toxic origin. This view is further corroborated by Baehr,[2] who has shown early perivascular infiltration and the late stages of thrombosis with aneurysmal dilatation in the same patient.

Summary. Widespread necrotizing arteritis is herewith described in a series of autopsies. There was no history of sulfonamide sensitivity or serum sickness in these patients. Sulfonamide therapy was used in the terminal illness. The vascular lesions were widespread, and are considered to be a specific reaction of blood-vessels previously sensitized by some non-specific toxin.

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EFFECTS OF LARGE DOSES OF A VITAMIN A CONCENTRATE IN NORMAL AND HYPERTENSIVE PATIENTS*

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Substances containing vitamin A, such as the non-saponifiable fraction of butter, have been shown to increase urea and inulin clearances in normal dogs and in dogs deprived of dietary vitamin A;[6,7] to increase the rate of glomerular filtration. Similarly, large doses of concentrates of the vitamin increased urea clearance in human beings.[8] Although the increase in inulin clearance specifies the change as one associated with increased rate of glomerular filtration, the mechanism of its increase remained unknown and it is part of the purpose of this study to determine its nature. It is also part of our purpose to examine critically the effect of large doses of a vitamin A concentrate in essential hypertension, since Govea, Peña and Villaverde[11,19] have recommended the use of the vitamin in this disease. In the first of these reports (1940) it is stated that, "of 65 cases, only 4 failed to show an impressive hypotensive effect," these being 4 cases of malignant hypertension with advanced renal lesions who, nevertheless, showed

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symptomatic improvement. In their second paper (1941) it is stated that of 100 patients treated, treatment was brilliantly successful in 25%, more or less noticeably effective in 50% and of no value in 25%. In an unstated number of patients the vitamin was given intramuscularly in oil with resultant local irritation, while in others it was given orally from the start, the doses used being 100,000 to 200,000 units initially, followed by a maintenance dose of half this amount. It is unfortunate that a report which promises so much in so important a disease should, by the absence of protocols which would establish the adequacy of the observations, fail to carry conviction. While our present study was in progress, Wakerlin, Moss and Smith[20] reported on the antipressor action of preparations containing vitamin A when fed dogs with experimental renal hypertension, an observation which gives additional interest to our clinical report.

Methods. The patients studied included 2 normal females, 1, otherwise normal, suffering from obesity, 14 patients suffering from essential hypertension and 1 in whom the disease was of malignant type. All had been previously observed in this clinic for months or years, so that chance variations in the levels of blood pressure and renal function were excluded as far as possible. Further, the enthusiastic (and frequently disappointing) subjective responses of many newly observed hypertensive patients to new régimes and new physicians were obviated by continuity of observation.

Measurements of blood pressure were made weekly, bi-weekly, or, in some, daily, in the prone position after 15 to 30 minutes rest in bed. The intensity of subjective complaints (headache, dyspnea, emotional instability) was charted on an approximately standardized basis to which reference has been made elsewhere.

Renal functional changes were observed by determinations of diodrast and inulin plasma clearances and diodrast Tm's in a manner substantially identical with that of Smith, Goldring and Chasis.[14] The plasma clearances and Tm's were calculated from means of 3 collections of urine. Plasma and urine inulin were estimated by the method of Corcoran and Page.[2] Diodrast-iodine was determined by a method which, in principle, consists of oxidizing diodrast-iodine in urine or plasma filtrates with bromine water, discharging the excess bromine with sodium formate and measuring photocolorimetrically iodate-iodine in the manner described for this determination by Flox, Piteski and Alving.[4]

The changes of cardiac output were found ballistocardiographically[17] in the manner described by Taylor and Page.[18]

The vitamin A concentrate used in this study, "Alphalin" (vitamin A, Lilly) was given orally in doses ranging from 100,000 to 400,000 units of the vitamin daily for periods of from 5 to 90 days.

Results. The results of this study may be considered first with reference to the clinical effect on arterial pressure and on the course of essential hypertension and, secondly, with regard to the effects of treatment on renal and cardiac function.

With regard to arterial pressure, treatment with vitamin A did not alter the mean blood pressure level or its range of variation in either normotensive or hypertensive subjects (Table 1). The treatment did not result in any change in the complaints of those of the hypertensive patients presenting symptoms of their condition, nor, on the other hand, in any untoward effect.

TABLE 1.—EFFECT ON ARTERIAL PRESSURE OF TREATMENT WITH VITAMIN A CONCENTRATE

Patient			Months prior obs.	Dosage (thous. U.)	Days treated	Arterial pressure					
						Before treatment			After treatment		
No.	Initial	Diagnosis				Lowest	Highest	Average	Lowest	Highest	Average
1	E. W.	Norm.	2	200	14	100/70	128/82	*120/78*	104/76	126/85	*122/80*
2	J. S.	Norm.	2	400	28	98/64	110/77	*108/76*	100/62	114/80	*106/72*
3	I. B.	Obese	6	100	14	110/70	120/90	*120/80*	108/68	124/88	*118/80*
4	J. B.	Ess. HT	24	100	28	182/114	220/150	*180/124*	176/116	190/126	*184/123*
5	G. B.	Ess. HT	18	100	14	200/120	240/142	*214/130*	220/136	220/150	*220/143*
6	H. B.	Ess. HT	72	200	5	160/100	220/130	*198/114*	178/96	224/128	*194/112*
7	R. G.	Ess. HT	37	400	18	156/90	184/116	*172/98*	180/100	206/120	*182/110*
8	S. H.	Ess. HT	60	200	39	190/102	244/124	*210/114*	190/106	220/120	*208/112*
9	V. L.	Ess. HT	72	200	41	182/100	220/108	*194/106*	180/96	204/110	*190/100*
10	L. P.	Ess. HT	15	200	57	158/98	200/114	*172/112*	156/96	184/118	*174/110*
11	P. R.	Ess. HT	6	200	25	158/104	194/124	*172/114*	158/96	200/120	*172/110*
12	N. S.	Ess. HT	5	400	28	166/90	240/140	*226/120*	166/94	250/122	*224/122*
13	C. T.	Ess. HT	85	200	80	140/80	186/110	*170/94*	142/76	184/100	*172/90*
14	E. T.	Ess. HT	80	200	90	190/100	266/154	*218/122*	198/90	246/128	*228/126*
15	N. Y.	Ess. HT	36	100	24	140/114	190/140	*178/128*	154/120	192/136	*177/130*
16	M. N.	Mal. HT	15	200	28	180/114	220/150	*210/130*	206/106	250/148	*208/140*
						For group **178/109**			For group **180/110**		

No. = case number; Initial = patient's initials; Norm. = normal; Ess. HT = essential hypertension; Mal. HT = malignant hypertension. Months prior obs. indicates the number of months during which the patient's blood pressure had been observed.

The effects on renal function were at once less consistent and more interesting than those on arterial pressure. The results of individual observations are tabulated in Table 2 and the net effects summarized in relation to dosage and duration of treatment in Table 3. Of 2 normotensive patients (Nos. 2 and 3) 1 (No. 2) showed a modest increase in plasma diodrast clearance during treatment. In the 1 patient (No. 16) suffering from malignant hypertension, secretory tubular mass (Tm_D) had decreased after 13 days of treatment without corresponding changes in the clearances of diodrast and inulin. On the 28th day of treatment of this patient renal function had greatly deteriorated and the disease progressed inexorably to death in uremia.

TABLE 2.—EFFECT ON RENAL FUNCTION OF TREATMENT WITH VITAMIN A CONCENTRATE

Patient No.	Day before during or after treatment	Dose (thous. units)	Clearance (cc. per 1.73 sq. m./min.)		Filtration fraction	Tm_D (mg. diodrast iodine per 1.73 sq. m./min.)	Total protein (gm./100 cc.)	Hemat. (%)	B.P. (mm. Hg)
			Diodrast	Inulin					
2	0 B	0	747	139	0.18	51.0	8.0	34	92
	28 D	400	857	148	0.17	53.0	8.4	38	97
	32 A	0	626	140	0.22	..	..	38	90
3	0 B	0	715	137	0.19	58.0	6.3	38	105
	14 D	100	663	140	0.21	..	..	43	105
4	0 B	0	344	107	0.31	39.4	6.8	45	161
	14 D	100	444	107	0.24	..	..	49	158
	110 A	0	384	123	0.36	..	..	50	153
5	0 B	0	366	95	0.26	37.0	6.6	39	161
	14 D	100	638	168	0.26	..	..	42	178
	90 A	0	589	123	0.21	..	..	36	157
6	0 B	0	..	..	..	21.9	7.3	40	154
	5 D	200	344	95	0.28	22.4	7.2	40	150
	5 A	0	299	84	0.28	..	..	41	153
7	18 D	400	831	192	0.23	51.3	7.1	39	145
	28 A	0	702	163	0.23	57.6	..	41	153
	48 A	0	550	183	0.33	42.9	..	37	156
8	0 B	0	364	102	0.28	37.0	6.7	44	179
	39 D	200	497	108	0.22	..	..	47	164
9	0 B	0	462	95	0.21	40.8	6.4	44	168
	12 D	200	426	84	0.20	43.0	..	41	156
	38 D	200	636	112	0.18	..	..	39	140
	15 A	0	534	132	0.25	..	..	39	135
10	0 B	0	474	87	0.18	31.7	7.1	30	125
	50 D	200	589	129	0.22	42.9	7.0	41	131
	21 A	0	525	121	0.24	52.3	8.3	43	184
11	0 B	0	590	145	0.25	46.8	6.1	38	140
	25 D	200	604	144	0.24	..	..	38	141
12	0 B	0	456	111	0.24	..	..	38	155
	28 D	400	483	129	0.27	52.0+	..	37	128
	20 A	0	436	98	0.22	49.0	6.9	40	156
13	0 B	0	624	137	0.22	55.0	7.0	41	122
	6 D	200	694	130	0.19	53.6	7.1	40	120
	31 D	200	660	144	0.22	51.0+	..	50	134
	30 A	0	671	183	0.27	65.5	7.1	39	136
	44 A	0	695	165	0.24	51.4	7.0	37	154
14	0 B	0	354	63	0.18	..	..	44	134
	0 B	0	321	59	0.18	23.9	6.0	45	134
	16 D	200	606	124	0.20	44.7	5.4	47	183
	33 D	200	568	120	0.21	..	..	45	139
	49 D	200	679	115	0.17	46.5	5.5	40	167
	50 A	0	668	107	0.16	43.1	..	38	187
16	0 B	0	137	50	0.39	16.2	6.1	45	175
	13 D	200	143	54	0.38	13.4	6.1	43	159
	28 D	200	88	17	0.20	..	..	48	152

Patient No. as in Table 1. Day of treatment indicated as 0 = control, B = before, D = during, A = after treatment with vitamin A. Tm_D = Secretory tubular mass. Clearances and Tm_D corrected to body surface area of 1.73 sq. m. per minute. Clearances in cc. per minute of plasma clearance and Tm_D in mg. diodrast-iodine (D–I) per minute. Total protein = plasma total protein, gm. per 100 cc. Hemat. = hematocrit index in per cent. B.P. = blood pressure on the day of observation in mm. Hg mean of systolic and diastolic pressure.

TABLE 3.—SUMMARY OF EFFECTS OF TREATMENT WITH VITAMIN A ON RENAL FUNCTION AND CARDIAC OUTPUT AS RELATED TO DOSAGE AND DURATION OF TREATMENT

			Percentile changes from control				
			Clearance				
Patient No.	Day of observation	Total dose U. × 10^6	Diodrast	Inulin	Filtration fraction	Tm_D	Cardiac output
6	5 D	10	+19	+13	0	0	+18
13	6 D	12	+11	−15	−16	0	+ 3
5	14 D	14	+74	+77	0	−	−
3	14 D	14	0	0	0	−	−
9	12 D	24	0	0	0	0	− 9
16	13 D	26	0	0	0	−16	+10
4	14 D	28	+29	0	−23	−	−
14	16 D	32	+90	+110	+10	+85	+18
11	25 D	50	0	0	0	−	−
13	31 D	62	0	0	0	(+20)	−
14	33 D	66	+70	+104	+16	−	
7	18 D	72	+51	0	−31	+29	+14
9	38 D	76	+39	+18	−15	−	−
8	39 D	78	+36	0	−20	−	−
14	49 D	98	+110	+96	0	+95	−
10	50 D	100	+24	+48	+20	+35	+ 8
2	28 D	112	+15	0	0	0	+12
12	28 D	112	0	+15	+12	0	−

Patient numbers and observation as in Tables 1 and 2. Accumulated total dosage of vitamin in 100,000's of units. The changes of diodrast and inulin clearances, filtration fraction, Tm_D, cardiac output (C.O.) and hematocrit index are recorded as percentile differences from control or (Patient 7) post-treatment levels. Differences of less than 10% in clearances or Tm_D were considered negligible in the tabulation. A dash (−) indicates that no observation was made. The bracketed ( ) observation of Tm_D in patient No. 13 was made 30 days after discontinuing treatment.

Among the 10 patients suffering from essential hypertension, all but 1 (No. 11) showed at one time or another increased clearances or tubular secretory mass. Diodrast clearance increased in 8, inulin clearance in 6 and tubular secretory mass (Tm_D) in 4 of 7 patients in whom observations were made. Because the increase in inulin clearance (rate of glomerular filtration) did not parallel the increase in plasma diodrast clearance (effective renal plasma flow), filtration fraction (ratio of inulin/diodrast plasma clearance) was unchanged in 3, increased in 2 and decreased in 5 patients. It is noteworthy that in 3 patients (Nos. 7, 10 and 13) the maximum increase in Tm_D was observed after treatment with vitamin A had been discontinued respectively for 28, 21 and 30 days.

Cardiac output as measured by the ballistocardiograph was determined in 1 normotensive (No. 2) and 7 hypertensive subjects before and during treatment. Cardiac output increased in the normotensive during treatment in association with an increase of plasma diodrast and inulin clearances of less than 10%. Among the hypertensives, cardiac output was unchanged in 1 (No. 13), although effective renal plasma flow had increased somewhat at the time of observation; in 6 other hypertensives, it was decreased in 1 (No. 9) in whom clearances had not changed and was increased in 5. In 4 of these 5 the increased cardiac output was associated with increased renal plasma flow as measured by plasma diodrast clearance. The increase of cardiac out-

put without increased renal plasma flow was recorded in the patient (No. 16) suffering from malignant hypertension and here note should be taken that the increased cardiac output was associated with maintenance of renal plasma flow and filtration rate at control levels in spite of decreasing renal tubular secretory mass (Tm_D), *i. e.*, there had developed a relative increase in blood flow to residual functioning tissue. In all 6 subjects whose cardiac outputs increased during treatment, the increase was due to tachycardia and was not accompanied by increased stroke volume.

Discussion. Although the presumed antipressor effects of preparations containing vitamin A were attributed to the action of the vitamin,[11,19] studies on the antipressor action of the vitamin in renal hypertensive dogs[20] have indicated that the effect is not one of the vitamin as such, since it does not develop after administration of the pro-vitamin, carotene, but rather persists after destruction of the vitamin A by irradiation. Harrison, Grollman and Williams[5] and Grollman and Harrison[5] have observed antipressor action of fish-oil concentrates in renal hypertensive rats which persists and may even be increased after destruction of the vitamin with CrO_3 or by irradiation. They have also demonstrated the antipressor ineffectiveness of the pro-vitamin (carotene) or of highly purified natural vitamin A concentrates. It therefore appears likely that whatever antipressor action preparations of the vitamin may have in renal hypertension in animals is due to some substance associated with the vitamin in the materials administered and not to the vitamin itself.

Our failure to observe antipressor effect in carefully studied cases of essential hypertension during the administration of large doses of the vitamin may be attributed to (*a*) the absence of the supposed antipressor substance which may accompany vitamin A in some concentrates and not in others; (*b*) some possible difference in the mechanism of experimental renal hypertension in animals and essential hypertension in man; (*c*) administration of insufficient quantities of the antipressor material or (*d*) accidental selection of refractory patients. However, considering these several possibilities, we note (*a*) to our best information the preparation of vitamin A used was of a type which should contain all that is present in many commercial preparations of the vitamin; (*b*) although their identity is not established, there are at least weighty analogies which link essential hypertension in human beings with experimental renal hypertension in animals; (*c*) the dose of the vitamin given by Wakerlin, Moss and Smith[20] was some 5 to 15 times greater than we have used in terms of unitage per kilo of body weight; (*d*) with 1 exception (No. 16) the patients suffered from rather mild and labile essential hypertension and should have shown improvement should such be possible with this method of treatment. It is therefore possible that our negative results as regards the effect of vitamin A on blood pressure may be due to the use of amounts too small to reveal effects observed in experimental hypertension with larger doses, although the amounts used were approximately equal to those given by Govea, Peña and Villaverde.[11,19] The use of much

larger doses and for longer periods would be almost prohibitively expensive in clinical practice. Nevertheless, we are continuing this aspect of the study.

The renal functional changes, *viz.*, increased renal blood flow, glomerular filtration rate and tubular secretory capacity for diodrast are of special interest. As this study was in progress, we were kindly informed that similar renal effects were under observation in normal dogs fed vitamin A concentrates.[1] The increased glomerular filtration rate observed by Herrin and Nicholes[7,8] is therefore evidently due to increased renal blood flow, although the cause of the renal hyperemia is still not apparent. Filtration fraction, which measures the relative level of intraglomerular pressure, is slightly more often decreased than not during treatment, which suggests that the increased renal blood flow is in part the result of efferent arteriolar vasodilation. But, since dilation of efferent arterioles at constant levels of arterial pressure and afferent resistance would result in increased blood flow without any change in filtration rate, it appears that with efferent vasodilation there developed a like change in the glomerular afferent arterioles, a view supported by calculation of our data according to the methods suggested by Lamport.[10] The fact that the vitamin preparation causes renal vasodilation suggests that this property, if it affects arterioles throughout the body, may be responsible for the antipressor effects observed experimentally in dogs and rats.

The increase in tubular capacity for diodrast secretion (Tm_D) was observed in patients treated with large doses and over long periods. In 3 of these it seems to have reached its peak after the vitamin had been discontinued and, in the 2 cases (Nos. 7 and 10) who had shown increased renal flow, after renal hyperemia had subsided. The increase in secretory capacity may represent either (*a*) an increase in the "concentration" of the hypothetical carrier substance responsible for transport of diodrast through the renal tubular cells or (*b*) an increase in cell mass. There is no evidence at hand to decide which factor prevails in this instance. The renotropic action of steroid hormones (reviewed editorially[9]) might bear on this decision were it not[21] that the increased secretory capacity provoked in dogs by administration of large doses of testosterone is not associated with concurrent changes in the rates either of renal plasma flow or of glomerular filtration, but is apparently due to local hypertrophy of the cells of the convoluted tubules.[12,13] The renotropic action of the steroid thus contrasts with that of the vitamin A preparation and the suggestion is made that the effect we observed may be the result of prolonged hyperemia rather than a trophic action of the vitamin or some concomitant substance.

The renal vasodilation which developed in most of our patients was not itself sufficient to cause a decrease in the level of arterial pressure, possibly because of the simultaneous increase in cardiac output. It is noteworthy that the increase in cardiac output under treatment with vitamin A is wholly the result of tachycardia, and thus resembles the effect of fever rather than the reduction of peripheral resistance occasioned in hypertensives by treatment with antipressor renal

extracts.[18] The action of the vitamin was not associated with increased oxygen consumption in 2 cases observed by Herrin and Nicholes.[8] Rather it appears that the cardiac action of the vitamin is a response to local renal vasodilation.

Even in patient No. 16 (13th day of treatment) whose renal tubular mass decreased by 18% as the result of nephrosclerosis, concurrently the residual tubular mass was perfused by an increased volume of blood. The increase in cardiac output was thus again associated with renal vasodilation although effective renal blood flow had not increased.

With regard finally to possible therapeutic use of preparations of the vitamin, the factor of cost of the large doses necessary to excite a renal response combines with its variable effectiveness to suggest that further study is necessary before it or some derivative or concomitant present in the preparation can be recommended. A similar variation in effect was noted by Herrin and Nicholes[8] and found *not* to be correlated to the plasma levels of vitamin A. With reference to hypertension, the absence of antipressor effect in subjects who showed improvements in renal excretory function is not surprising, since it is our view that the pressor and excretory aspects of renal function are distinct and, in large measure, independent.[3] The results do indicate that large doses of vitamin A may have therapeutic value in states of renal insufficiency and degeneration not primarily due to essential hypertension, as, for instance, in Bright's disease. This aspect of its use is now under study.

Summary. Administration of doses of a preparation of vitamin A in amounts ranging from 100,000 to 400,000 units daily for from 5 to 90 days in 3 normotensive and 14 hypertensive patients did not alter the levels of arterial pressure. Observations of renal function in 2 normotensive and 11 hypertensive patients revealed increased effective renal blood flow in 9, increased glomerular filtration rate in 7 and increased tubular secretory capacity for diodrast (Tm_D) in 4 of 7 hypertensive patients in whom this function was tested. The increase in effective renal blood flow was usually associated with increased cardiac output, the result of tachycardia and not of increased stroke volume.

Conclusions. 1. Vitamin A concentrate is ineffective in the treatment of essential hypertension in doses of 100,000 to 400,000 units daily for from 5 to 90 days.

2. The vitamin concentrate causes renal vasodilation and increased functional capacity for secretion of diodrast with increased cardiac output. The suggestion is made that it may have application in the treatment of degenerative renal diseases.

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Since this manuscript was submitted a complete report by Wakerlin and Moss (Proc. Soc. Exp. Biol. and Med., **53**, 149, 1943) has emphasized the point of view that antipressor activity is characteristic of some, but not all, vitamin A concentrates tested in renal hypertensive dogs. The details of the procedure used to determine diodrast iodine will appear shortly in the Jour. Lab. and Clin. Med.

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THE MEDICAL USE OF THIOCYANATES IN THE TREATMENT OF ARTERIAL HYPERTENSION*

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Review of Earlier Work. Although Claude Bernard[12] in 1857, made the first report on the pharmacologic actions of thiocyanate by demonstrating its depressant action on the animal heart, up to 1926 the majority of the experimental work on the medical use of thiocyanate was carried out in Germany.

In that country, Edinger[25b] in 1900, as quoted by Nichols,[61] treated satisfactorily a number of hypertensive patients with thiocyanate. Three years later, Pauli[65] got pleasing results in arteriosclerosis and hypertension, and Westphal and Blum[82] (1926) reported favorable results in another large series of hypertensive patients.

This last report stimulated investigators outside of Germany, among the most important of whom was Barker,[9] who in 1936 utilized the method of Schreiber[73] to measure the blood thiocyanate of patients under thiocyanate therapy. He found that the blood level was the important criterion for effective therapeutic dosage and for the prevention of toxicity. In 1941, Griffith *et al.*[37] described a micro method for determining blood thiocyanate levels, which considerably simplified the situation and he also suggested criteria for the selection of suitable patients.[38]

The Pharmacologic Actions of Thiocyanate Related to Its Use in Arterial Hypertension

A. **Pharmacodynamic Actions.** 1. ON THE CENTRAL NERVOUS SYSTEM. *Sedation.* Bernard[12] suggested and found a sedative action by thiocyanate. Pauli[65] confirmed this and went on to try the drug on hypertensive and

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nervous patients. Smith[75] classed it as a mild hypnotic and sedative. Symptoms varying from drowsiness and weakness to psychoses are reported.[11,13,38,42,54,71,79] However, there is little mention of this soporific action in the most recent literature. Goodman[35] ignores it completely and Nichols[61] could find none, although he expressively looked for it. Fineberg[28] also found none. In paradox, Bancroft[7] suggests thiocyanate to counteract the narcotics, due to its ability to prevent the precipitation of protein.

Irritation of the Anterior Horn Cell. Wald *et al.*[79] reported that dogs dying from thiocyanate poisoning went into hyperirritative states, as in strychnine poisoning. They assumed this to be a result of anterior horn cell irritation. Nichols[61] confirmed their statement that the pre-death stage was one of increased motor excitability. However, Jahr[43] injected thiocyanate into a dog's 4th ventricle without causing hyperirritability.

2. On the Muscle. *Paralytic Action.* Bernard[12] compared thiocyanate to curare in its effect on muscle. It paralyzed a frog's leg, but the contralateral reflex was not lost. The drug must be injected intramuscularly or cutaneously for this effect. Setschenow[74] noted the same paralytic effect, but claimed a skin anesthesia came first. Weakness is one of the commonest toxic symptoms of thiocyanate overdosage,[29] but whether this is from actual paresis or a subjective reaction is a matter of question. Jahr[43] found the fatigability of a rabbit's tibialis was increased when perfused with thiocyanate. He quotes Taubman and Heilborn[76b] as finding the same result in isolated muscle. Westphal[82] reported that there was no relaxation of arterial muscle if it was immersed in thiocyanate solution. Adrenalin would still cause a contraction in the muscle in the solution.

Stimulation of Smooth Muscle. Kotte[45] quotes Ellinger as finding increased tone in isolated arterial strips immersed in thiocyanate solution.

3. On Blood and Vascular Organs. *Decreased Viscosity.* Doles[25a] reports that patients with macrocytosis have a decrease in cell volume after treatment with thiocyanate. The total serum protein has been found decreased.[11] The albumin globulin ratio has been reduced by thiocyanate.[82]

Vasodilation. Goodman[35] gives a relaxation of smooth muscle as one of the effects of thiocyanate. Griffith[38] believes the drug releases a spasm of the arterioles, because it will often increase the cutaneous lymphatic flow, and because the best effects in the treatment of arterial hypertension are obtained in patients whose arteries are without organic change. Bernard[12] said thiocyanate would increase the diameter of a vessel in a frog's mesentery. Westphal[82] confirmed these findings.

However, Robinson[69] could find no evidence of peripheral dilation in the arteries or arterioles. Kotte[45] with Karl Smith found no vasodilation by perfusing thiocyanate through an isolated rabbit's ear. I also found no increase in the peripheral blood flow of cats as measured by the themostrohmur, the blood thiocyanate level being gradually raised until death ensued.

Hypotensive Effect. Since the first suggestion of its use to treat hypertension by Pauli,[65] this effect of thiocyanate has been in question. Goldblatt[33] found that a toxic level was needed to produce a blood pressure fall in hypertensive dogs. Grollman *et al.*[39] found no significant blood pressure fall in rats, with oral dosage. Barker and Davis[10] demonstrated that sympathectomy sensitized the patient to thiocyanate, so that a small dose would create the same hypotensive effect after operation that a large one would, prior to operation. Kurtz[46] confirmed this. Hamilton[41] found no

significant drop in blood pressure in dogs treated with thiocyanate. Nowhere in the literature could I find a mention of a hypotensive action in a laboratory animal, except when it was quite toxic. Quattlebaum[66] took 9 gr. q.d. for 1 week and there was no change in the blood pressure, except for a transient 10 mm. drop in systolic pressure on the 7th day. The author makes no mention of any subjective symptoms.

However, the majority of clinical authors believe there is a definite hypotensive effect in a large percentage of cases of arterial hypertension. This will be discussed later.

Hypertensive Effect. Lodholz[48] found a blood pressure increase terminating in death, in dogs fatally poisoned with thiocyanate. Setschenow[74] had also found this action. I found the same phenomena in dogs and cats prior to exitus from thiocyanate.

Cardiac Depression. Bernard[12] noted that the heart was depressed and stopped beating when he injected frogs and rabbits with thiocyanate. The cessation was in diastole, but he was unable to determine whether this was a result of muscular weakness or lack of excitation. Paschkis[64a] reported that heart block was caused by the drug in frogs, and would be relieved by atropine. Nichols[61] says it depresses the normal heart.

However, Massie[52] reports that there is no change in the EKG with thiocyanate. Starr[76] says the cardiac output in a good many conditions that he studied often actually increases as the blood pressure goes down. Several authors have actually found a decrease in heart size upon dosage with the drug.[11,46,84]

Depression of the Blood Cholesterol. Askanzy[2] has said that thiocyanate decreased the blood cholesterol. Lodholz[48] quotes Monk in saying that the liver is the storehouse for thiocyanate. He blames the decreased cholesterol on liver function depression.

Respiratory Stimulation. Paschkis,[64a] as quoted by Nichols,[61] reported a respiratory increase with thiocyanate; Jahr[43] denied this. I found a similar effect in cats, upon the intra-arterial injection of sodium thiocyanate. However, I found the same effect after the injection of sodium chloride solution. Thus I attributed the stimulus to a non-specific irritation of peripheral nerve endings in the limb. Comroe[20] injected the region of the carotid body and found no respiratory changes.

4. On Glands. *Mucus Glands.* Goodman[35] described the action of thiocyanate as increasing the mucus flow, in the manner of iodine. Pauli[65] said it would lead to a rhinitis. Mayer[54] reported rhinorrhea in patients treated with the drug; Takacs[76a] said it increased the stomach secretion.

Endocrine Glands. Wald *et al.*[79] found in their patients, after treatment with the drug, that a goiter occurred that improved with iodine. Barker[9,11] found thyroid enlargement and facial myxedema in some of his patients while under treatment. Pauli[65] said thiocyanate was harmful on top of thyroid dysfunction. He also stated that thiocyanate does not pass through the body without affecting the endocrines. Kobacher[44] presented 1 case in which symptoms of thyroid dysfunction were produced by the drug, and relieved by its omission. The woman's hearing was depressed during the existence of the thyroid lesion, but returned following cessation of the drug. Webster says "a cyanide" is the factor leading to the production of the experimental "cabbage goiter." Fahlund[27] reported a case of painful enlargement of the thyroid in less than a week of thiocyanate treatment. He believed it was an instance of sensitivity.

Healy[42] tested the adrenals of thiocyanate dosed rabbits and found a high concentration of the drug in that organ.

5. On the Kidneys. *Diuretic Action.* Westphal[82] reported 3 cases with increased renal function in spite of decreased blood pressure. Nichols[61] found a diuretic action in rabbits. Healy[42] noted a diuresis and thiocyanate-uria in rabbits. Barker[11] found diuresis as a toxic symptom. Jahr,[43] however, found renal damage in rabbits resulting from the drug.

6. On the Liver. *Depression of Liver Metabolism.* Major[51] reported a decrease in the blood guanadine bases. Damage to the liver and bone marrow as seen in benzene poisoning has been found.[11] Robinson[69] found the metabolism of the liver decreased as much as 40%, as measured in the Warburg apparatus, with a thiocyanate. concentration of 20 mg. per 100 cc.

B. **Toxic Actions of Thiocyanate.** 1. On Patients. There appear to be toxic effects directly from the action of the drug, and secondarily, from the decreased blood pressure. They will be taken up in that order.

Direct Effects of Moderate Severity, With Low Blood Levels. A blood concentration of 12 mg. per 100 cc. or less is regarded as low. Doles[25a] gives the basis for this classification. Weakness and fatigue are reported in this concentration range.[2,11,31,38,53,54,69,79] Doles[25a] says these symptoms will often go away spontaneously at the end of 2 to 6 weeks of therapy. A dermatitis of the erythematous type, with or without pruritus.[13,69,71] is sometimes seen. Also a maculopapular eruption of the seborrheic areas of the chest and back.[65] Gager[31] and Kurtz[46] reported dermatologic lesions of the face and corners of the eyes and mouth. Somnolence has been reported,[9,75,79] but is usually in the higher concentration group. Nausea is reported.[13,54,64] Griffith[38] says nausea can be reduced by diluting the solution. Mayer[54] used enteric coated capsules.

Direct Effects of Greater Severity With Greater Than Therapeutic Blood Levels. Gastric hemorrhage was noted by Nerking;[60] Franz also found this. Vintilesco[78a] is quoted as saying that his fatal case had gastric necrosis at autopsy. Purpura has been reported;[59,69] also a decrease in libido;[31,69] nervousness;[9,38,64] and bloody diarrhea.[13]

Mental symptoms are prominent in this group. Hallucinations,[42,69] slurring speech, unsteady gait and disorientation[11] have been recorded. Mandibular neuritis, with a questionable relation to thiocyanate, has been reported.[13]

A severe complication of thiocyanate treatment is exfoliative dermatitis, which clears up, if at all, rather slowly after cessation of medication. Alopecia often accompanies it. Cases of exfoliative dermatitis have been reported by numerous authors.[5,61,69,78,80] Pyrosis, anorexia and nausea are an index of high or increasing thiocyanate level.[79]

Sensitivity to Thiocyanate. Fahlund[27] describes a case of acute "thyroiditis," which he ascribes to sensitivity to thiocyanate. Thiocyanate sensitivity may be responsible for many of the toxic symptoms, for the tolerance varies greatly from person to person. Griffith[36] finds a small percentage of persons who exhibit a toxic reaction to their first small dose of thiocyanate and attributes this to a sensitivity.

Indirect Toxic Effects of Thiocyanate Due to the Fall in Blood Pressure. An anginal attack in an elderly patient without any previous history of angina has been reported[69] during thiocyanate treatment. The same author also reports another patient with increase in anginal attacks after thiocyanate. Other reports of anginal pain during thiocyanate therapy exist.[46,64]

In discussion of these cases in relation to the thiocyanate treatment of hypertension, several points should be made. First, Barker[9] has shown that the drug should not be used without knowing the blood level. In

only 2 of these cases was the blood level known; therefore, the remainder should be discarded in a strict consideration of its toxic effects. It is obvious that the first 3 cases do not reflect discredit on the medicinal use of thiocyanates. Second, Hamburger's case was not reported as a true death from thiocyanate, the drug being postulated only as contributory.

TABLE 1.—SUMMARY OF RECORDED FATALITIES

Reporter	Sex	Age	Date	General
Lesser (see Russell[71])	M	58	1898	Suicide
Kobert (see Russell[71])	F	..	1906	5 gm. of drug
Vintilesco and Popesco[78a]	M	27	..	100 gm.
Healy[42]	F	63	..	5 gr. t.i.d.
Goldring and Chasis[34]	F	40	1932	10 gr. per day
Ibid[34]	F	56	1932	12 gr. per day
Saleeby[72]	..	..	1931	Died after acute respiratory inf.
Garvin[32]	F	71	1941	Blood level 18.7
Hamburger[40]	M	..	1941	30 gr. in 7 days; was in hypertensive encephalopathy
Russell[71]	M	52	1942	Blood concentration greater than 21 mg. per 100 cc.; urea clearance 27%

In both of the cases where the blood level was known, it was high. Barker[9] recommends an 8 to 12 mg. per 100 cc. level, certainly no higher than 15 mg. per 100 cc. The last case also had a low urea clearance. In spite of this, these 2 cases clearly died from the effects of thiocyanate.

Experimental Work on Thiocyanate Toxicity. The potassium salt is 5 times as toxic as the sodium salt when injected intravenously in animals; but there is no difference per oris.[1] However, Westphal[82] said the potassium salt is more potent as a hypotensor, even when given per oris. This has not been confirmed,[71] but rather repudiated by the indiscriminate use of either salt without noticeable difference. There were no uniform lesions found in dogs poisoned with thiocyanate.[2] Laufer postulated that the hyperirritability found in poisoned dogs might result from hypocalcemia. However, Jahr[43] produced convulsions even when calcium was injected along with the thiocyanate. Healy[42] put forward the idea that all the toxic symptoms might be from hypo-adrenemia, as he noted a concentration of the drug in that organ. Griffith[38] attributes the dermatitis and diarrhea to idiosyncrasy. Fineberg[28] found some gastric irritation from thiocyanate. Jahr[43] produced weight loss in dogs, cats and porpoises with the drug. He regarded this as a result of gastric mucosal irritation, producing diarrhea. The drug caused albuminuria and hematuria in rabbits. Diarrhea, central nervous (spinal cord) irritability, spastic paresis, opisthotonus, cramps, and death are the progressive symptoms of fatal thiocyanate poisoning in animals. Thiocyanate does not convert to cyanide in the body.[75] However, Nerking[60] says prussic acid can be produced in the mouth from caries, sodium chloride and thiocyanate.

The Clinical Use of Thiocyanate in the Treatment of Arterial Hypertension and Results

A. **The Clinical Use.** *Dosage.* Before Barker's[9] report on the necessity of determining the blood level of the drug, many empirical dosage methods were advised. In the light of our present knowledge, the actual dose is not as important as the blood level. Goodman[35] recommends a 0.3 gm. (5 gr.) dose per day. Griffith[36] recommends a 0.2 to 0.4 gm. dose per day initially and a blood thiocyanate level taken by at least the end

of the first week. The following doses should be entirely regulated by the blood level. The micro method of Griffith[37] is the most practical for frequent thiocyanate blood level determinations. The blood level of 15 mg. per 100 cc. should never be exceeded. Barker[9] recommends a level between 5 to 6 mg. per 100 cc. at first. If there is no benefit, raise it to between 8 and 12 mg. per 100 cc. Blood thiocyanate levels of 40 to 60 mg. per 100 cc. without untoward symptoms have been observed.[18]

Route. No mention of any other route than oral for the routine treatment of hypertension with thiocyanate was found in the literature. Freeman[30] recommends enteric coated capsules to prevent gastric upsets. Griffith[38] reports that diluting has decreased gastric irritation in his experience.

The Salt Used. There has been no confirmed evidence in the literature of the advantage of one salt over the other. Sodium thiocyanate and potassium thiocyanate are used almost equally in the reported cases.

Tolerance. No tolerance has been noted.[19] No other mention of tolerance was found in the literature.

Latent Period. No beneficial effects from the drug appear for at least a week. The effects may last 2 months after the drug is stopped.[15] The drug may be retained until about the 6th day.[23] Dogs retain toxic effects for around 2 weeks.[33]

Distribution of the Drug in Body Fluids. Thiocyanate is not evenly distributed to all parts of the body, but does reach an equilibrium with the body fluids in about 2 hours.[23] It is not, however, distributed to the cerebrospinal fluid.[45]

Indications and Contraindications. Griffith advises the use of thiocyanate only in selected cases[38] of hypertension with some degree of capillary mobility or reducible spasm. This is in contrast with the general opinion, which seems to be that one should use thiocyanate in any hypertensive individual unless it is contraindicated.

Kidney, heart damage, cardiac decompensation, and general inflammatory conditions have been given as contraindications.[49] Acute nephritis and renal insufficiency are proposed.[19] As a general principle, patients with renal retention and poor clearance are more liable to radical toxic effects, either from increased blood concentrations, or damage to the kidney *per se*.[11,82] However, Kurtz[46] says that chronic nephritis is no contraindication, and other authors[52,56] say albuminuria is no contraindication. Toxic symptoms are more frequent in advanced age[42] and some workers advise that a patient who is more than 60 should not take the drug.[52,56,69] A good heart and relatively normal BUN are a necessity.[52] Thiocyanate will have a harmful effect in toxemia of pregnancy.[19] Patients with advanced arteriosclerosis do not respond well to the drug.[8,14,69] Logefeil[49] gives a complete list of contraindications including all hypertensive states except essential arterial hypertension without sclerosis. He contraindicates the drug in inflammations of the upper respiratory tract, as it will cause further irritation. The drug is recommended as a preoperative medication for sympathectomy.[21]

B. **Results From the Use of Thiocyanate in the Treatment of Hypertension.** *Results in the Pre-Barker Epoch.* The majority of authors writing prior to 1936[2,14,15,28,31,33,49,50,52,56,62,63,65,72,75,82] were in favor of the use of thiocyanate in hypertension. Some[3,4,5,34,57,64,67,81] regarded the drug as too toxic, and one thought there was little or no specific hypotensive action.[3]

In general, the authors who found good results, got a drop of systolic blood pressure of 30 to 40 mm. of mercury and a diastolic drop of 10 to

15 mm. of mercury or more. They were satisfied that the toxic manifestations, if they did occur, were justified by the results obtained.

The Post-Barker Epoch. The majority of the authors are still in favor of the use of thiocyanate, by a greater margin than before 1936[8,9,11,13,16,18,22,24,25a,29,37,38,45,46,52,54,55,66,68,69,77,79] The greater part by far of this group regulated the drug dosage by watching the blood level. Some reporters still feel the treatment is not worth the danger.[6,25,26,32,33]

Goldblatt[33] is doubtful of the existence of the hypotensive effect, as it has never been demonstrated in a laboratory animal without marked toxicity. None of the clinical reports have completely eliminated all the variables which might cause unrelated blood pressure variation. Robinson[70] reports normal blood pressure variation in the region of 10 mm. per week at 120 mm. and it is even greater at higher pressures. It would be difficult to design an experiment which would take such an order of variation into account.

Theories of the Hypotensive Action of Thiocyanate in the Hypertensive Patient

A. **Decreased Cardiac Output.** *Through Cardiac Depression.* Bernard[12] said he found depression of the animal heart from thiocyanate. In my animal experiments, the heart action was not depressed until immediately before death. Thiocyanate has been contraindicated in cardiac failure,[75] but no note has been found in the literature of cardiac failure being produced or intensified by the drug. The electrocardiogram shows no changes after thiocyanate administration.[53]

Through the Endocrines. An effect through the endocrine system has been suggested by Healy[42] who found increased thiocyanate in the adrenals after drug dosage. He postulates hypoadrenemia leading to a blood pressure fall. Hypothyroidism[9,11] might result in the blood pressure drop.

Through Decreased Venous Return. The muscular paralysis reported by Bernard[12] would lead to this effect.

B. **Decreased Peripheral Resistance.** *Through Vasodilation.* This has been discussed under the pharmacodynamic actions of thiocyanate. Westphal[82] expresses the general opinion of the German authors, that the blood cholesterol was increased in the majority of their hypertensive patients, and that they employed thiocyanate to decrease it. According to their theory, the sterol decreases the permeability of the smooth muscle cell wall, leading to constriction of the arteriolar vessels. The drug would counteract this, by decreasing the cholesterol concentration.

Through Decreased Blood Viscosity. Doles[25a] reported a decrease in erythrocyte volume of macrocytic patients with essential hypertension when they were given thiocyanate. Similarly, Jahr[43] stated that thiocyanate did not decrease the red blood cell count, but did decrease the hemoglobin content. Taubman,[76b] however, says that thiocyanate did decrease the blood count in his experience.

A decreased blood protein, or altered alb/glob ratio would change the serum viscosity.[82] There is also the possibility that the cohesion of the cells in the blood might be varied.

Through Removing Calcium Deposits. Pauli[65] thought he was removing calcium from the arteriosclerotic vessel walls with the drug. Leroy[47] used thiocyanates to dissolve cataracts with the same thought in mind.

C. **Decreased Blood Volume.** Jahr[43] suggested that a shift in the water balance *via* the endocrines might be the basic cause of some of the

good and bad effects of thiocyanate. No other mention in the literature of a change that could be related to blood volume was found.

D. **Miscellaneous.** Meakins[57] suggests that an effect on tissue oxidation might cause the hypotension. A depression of liver metabolism has been mentioned before.[69] A decrease in the guanidine bases has been found with thiocyanate treatment,[51] and has been suggested as the basis of the blood pressure fall.[75] Edinger put forward the increase in nitrogen and sulphur excretion as the cause. The rationale is obscure.

In general, sex, age, retinal lesions, urinary findings, myocardial damage, orthodiagram, cytologic findings and serology show no relation to the hypotensive effect.[15,58] It should be noted that actually some of the subjective effects for which thiocyanate is given also appear to be caused by it.

Conclusions as to the Use of Thiocyanate in the Treatment of Hypertension

The majority of clinical workers believes that thiocyanate has a definite hypotensive effect in the arterial hypertensive patient. However, this hypotensive effect has not been demonstrated in the laboratory. The mechanism by which this clinical blood pressure drop occurs is not known. It is to be hoped that a complete statistical analysis will be done in the future to prove this suspected hypotensive effect.

A satisfactory method for the administration of thiocyanate has been suggested by Barker[9] which will give minimal toxicity if handled correctly. Thiocyanate should never be given without blood levels being taken. Thiocyanate is not a blanket cure-all for "hypertension" and should be used only in selected cases and where no contraindication exists.

Any relief of subjective symptoms bears minimal relation to the blood pressure drop.[2,3,13,68]

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VITAMIN E AND ITS RELATION TO REPRODUCTION*

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In 1923 Evans[40] first announced a dietary constituent that was necessary for normal reproduction in rats. He at that time showed that without this constituent male rats were infertile due to damaged epithelium, and females failed to carry their young to term. Since then we have advanced

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far in our knowledge of this substance; it has been taken apart, synthesized, and various deficiency diseases have been produced in animals which were then cured with this substance. Yet we know very little about its actual workings in the human body. The attempt is made here to assemble salient features which have come to light during these past 20 years from study of this substance, which is called vitamin E.

Space forbids reviewing the entire field at this time, hence this paper must be limited to the part played by vitamin E in relation to reproduction. Its rôle in the muscular dystrophies, amyotrophic lateral sclerosis, malignancy, and so forth, must be entirely omitted. For a brief review of these aspects see Mason.[58a]

The active principle of vitamin E has been thought to be associated with anti-oxidants since Olcott and Mattill[69–72,75] first showed the substance present in lettuce oil. Later, Bradway[17] showed that it is present in tomatoes, carrots, and wheat germ oil and is accompanied by inhibitors which prolong the induction period of auto-oxidizable fats.

Vitamin E has been shown to be a durohydroquinone.[43,61] Evans[41,42] prepared from the unsaponifiable portion of wheat germ oil a fertility potent factor which is known as alpha tocopherol, a reduced polycylic compound of the sterol type. He produced an alpha and a gamma fraction from cottonseed oil; only the alpha fraction is obtained from lettuce.

Other studies[12,14,29,31,35,43,47,61,71,73,95,97–99,104] on the biologic aspects of the chemistry of vitamin E will not be considered here, suffice to say that: (1) Absorption spectrum analysis shows a band at 2940 Ångstroms[54,71] which is not connected with the activity of the vitamin.[29,66,70,71,73] (2) It is stable to light and heat. (3) It is destroyed by bromination, ozone, perbenzoic acid, potassium amide, and so forth.[72,112] (4) Concentrates cannot be hydrogenated. (5) Alpha tocopherol (a 6-hydroxy chroman) has been synthesized.[95,97]

Bioassay. Vitamin E may be assayed by keeping adult female rats on an E deficient diet and noting the ability to bear living young following administration of varying amounts of concentrates by mouth. Bacharach[14] showed that failure to mate, failure to ovulate or failure to implant was not related to the amount of vitamin E present. He suggests[13] that biologic activity of a sample of vitamin E should be taken to mean its content of tocopherol, not its effect on vitamin E deficient rats.

Palmer,[79] using single oral doses, found that the correlation between live litter efficiency and placental implant was significant. At best, however, the assay is qualitative. He found a high retention of vitamin E in processed wheat germ oil kept 1 year at room temperature in sealed cans.

Makenzie[51] recommends the use of rabbits in estimating the content of vitamin E necessary to cure muscular dystrophy. Emmerie[37] described a colorimetric method of identifying and assaying tocopherols. Mason[56] has proposed assay by the uterine index method, which is the weight of uterine contents in grams plus the number of viable fetuses at term divided by 5. Mason[58c] in a new and rapid method to bioassay vitamin E bases his values on the number of live fetuses and the weight of uterine contents at the 16th day of pregnancy. The presence of 2 or more viable fetuses *in utero* at the 16th day of life affords criteria of positive response equal to, and in certain cases more reliable than, that based on delivery of progeny at term. He states that there are other advantages to be gained from this shorter test period in the bioassay, namely the economy in animal care and diet, and the information gained by examining the uterus as to atypical states, and positive responses.

It has been recommended by the members of the International Vitamins Standardization Conference that synthetic racemic alpha tocopherol acetate shall be adopted as the International Standard for vitamin E.[48b] The International Unit has been defined as the vitamin E activity of 1 mg. of the Standard Preparation. This is the average quantity which prevents resorption of gestation in rats deprived of vitamin E when the substance is administered orally. The strength of the Standard Solution is such that 1 gm. contains 10 International Units (or 10 mg. of alpha tocopherol acetate). The standard has certain physical and chemical properties which are described in the literature.[48b]

Relation to Other Biologic Products. Adamstone[7] has shown the relation of vitamin E to anthracene and its derivatives. He believes that it is just as necessary for the normal utilization of anthracene substances as vitamin D is for calcium and phosphorus.

Cholesterol, an anthracene substance, disappears from the brains of young chicks along with degeneration of the brain when these chicks are kept on vitamin E free diets. In muscular dystrophies due to vitamin E deficiency, the cholesterol content increases. Vogt-Møller[110] has reported hypocholesteremia in pregnant women subject to habitual abortions.

Calciferol, also an anthracene substance, when used in the form of cod-liver oil to supplement a vitamin E free diet, produces a lymphoblastoma, whereas halibut oil produces an erythrophagocytosis.

Androgen, the anthracene substance from the testes, needs vitamin E for normal utilization, as shown by Adamstone[4] using caponized fowl.

Pituitary gonadotropin and vitamin E play different rôles. Vezar[108] showed an abundance of vitamin E had a stimulating action on the sexual cycle. He can induce precocious maturity in young females but requires the presence of ovaries. Vitamin E cannot be substituted for in vitamin E free diets by estrin, progesterone, or anterior pituitary extract. Most evidence favors vitamin E as essential for the normal functioning of the anterior lobe of the pituitary. Changes in the pituitary gland will be discussed under Pathology.

Moore[65] showed that vitamin E deficiency also decreased the reserves of vitamin A. Shute[93a] has shown that neuritis in pregnant women due to vitamin B deficiency was $2\frac{1}{2}$ times more frequent when associated with a vitamin E deficiency.

Physiology and Pathology. *Production of Vitamin E Free Diets.* There are several methods which can be used, namely: (*a*) By adding cod-liver oil, butter fat, or lard to the diet; *i. e.*, oxidation by fatty substances.[69–77] (*b*) By treating the diet with ferric chloride; this produces sterility in 12 weeks in rats.[113] All the germinal epithelium is lost, and all the fetuses in the first gestation are resorbed. (*c*) Drying is a necessary factor for inactivating vitamin E. (*d*) Possible destruction of vitamin E by other fats in diet was suggested by Mattill.[59]

Relation to Growth and Development. Martin[54] says that vitamin E increases early growth. However, Olcott and Mattill[74] concluded that the improvement in early growth was not due to vitamin E.

That vitamin E may be a factor in the hatchability of chick eggs was shown by Adamstone,[8] because fertile eggs produced by pullets fed on vitamin E deficient ration failed to hatch a normal amount of healthy chicks. Embryos from eggs on a vitamin E free diet usually died by the 4th day of incubation. The pathologic conditions causing death were: (*a*) degeneration of the circulatory system; (*b*) hemorrhages and groups of histocytes; (*c*) a lethal ring in the blastoderm which surrounds the embryo

and causes death by starvation, asphyxia, and general toxemia. Barnum[16] showed that adding 15% wheat germ oil to the diet gave normal eggs.

Cunningham and Hopkirk[22] found that diets high in protein or low in protein produced good growth but induced sterility by damaging male germinal epithelium resembling vitamin E deficiency. Vezar[108] showed that normal rats started their estrous cycles at an average body weight of 100 gm., but vitamin E deficient rats began their cycles at weights averaging 30 gm. Emerson[36] says there is a response to wheat germ oil after a plateau in weight has been reached. The growth stimulating factor is in the non-saponifiable portion. Olcott[77] says that rats on a vitamin E free diet grew as fast as those on high vitamin E diets, and supported the claim that early growth is not due to vitamin E. Goettsch[44a] reared 7 generations of mice on vitamin E low diets and found no retardation in growth.

Hormone Balance. Nelson[68] showed that the male hypophysis from vitamin E deficient rats was more potent in the gonad stimulating hormone than from normal rats, but less potent than from glands of castrates. Others[82] have shown that anterior pituitary extract or pregnancy urine do not prevent resorption of embryos in vitamin E deficient females and that pituitary deficiency is not the primary cause of resorption. After castration the basophil cells of the anterior pituitary are altered and the gonadotrophic potency of whole gland increases. This is in disagreement with Nelson.[68]

Singer[94] says the thyroid is hypoplastic and Underhill[106] confirmed this finding in vitamin E deficiency. The latter also described changes in the anterior lobe of the pituitary; namely, the acidophils are small and degenerate and have pyknotic nuclei and the cytoplasm stains poorly. Also there is a degeneration of the basophils with a decrease in gonadotropin. No evidence of histologic changes and no castration cells have been found in pituitaries of vitamin E deficient females, as have been claimed for the males. The thyroid of male rats kept on vitamin E deficient diets for periods of 6 to 15 months showed more histologic activity and weighed more grossly than normal controls of the same age and sex. An increase in the BMR was found also. However, these effects were found to be due to deficient iodine content in the water rather than the lack of vitamin E, for by increasing the iodine in the diet to normal, the thyroids became normal and the BMR returned to normal.[16a]

Effect on Female Reproductive System. It was Evans[40] who first pointed out the "resorption" of the fetus in pregnant female rats kept on certain diets, which we now know to be lacking in vitamin E. Since then, many have reported the effect of vitamin E in increasing the number and viability of the litter. Evans,[40] however, in a review of the literature, states that large amounts of vitamin E do not improve reproduction beyond normal limits, and that large amounts during the first gestation will protect a second, even though on vitamin E free diets, but not a third gestation.

Its necessity for the embryonic growth in animals other than the rat and mouse is being established; for example, Vogt-Møller[110] injected 20 cc. of sterilized wheat germ oil into cows which had repeatedly failed to become pregnant and as a result 33 out of 50 cows so injected became pregnant. Schioppa[83a] found large doses of wheat germ oil increased litter size, and in the diet of sows, the mortality of suckling pigs was reduced.

Subcutaneous injections of vitamin E have no effect on the ovaries, uterus, the opening of the vagina or cornification of the vagina in imma-

ture female rats.[71] Urner[107] found intra-uterine changes, namely, a gross purplish discoloration and congestion of normal pregnancy. After the 12th day, no normal uterus and no embryos were found. Histology remained normal until the 10th day. Moore[64] found a brown discoloration with pigment in the muscle cells.

In rats, injection of estrogens or anterior pituitary extract will not substitute for vitamin E in deficient diets. Szabo[103] showed that vitamin E caused uterine hypertrophy in pseudopregnant mice but not in normal mice. Histologically this hypertrophy is seen to be due to an increase in connective tissue and muscle fibers. McCullagh[62] and Marchesi[53] observed no histologic changes in ovaries of vitamin E deficient females and also there was no direct effect on the vagina, the non-gravid uterus, nor on fertilization and gestation; however, the pregnancy was terminated by resorption of the fetus.

Effect on Lactation. Evans[39] says other factors are necessary for lactation beside vitamin E. Sure[102] attempted to prove that vitamin E is made up of two fractions, one for fertility and one for lactation, but concluded that no specific vitamin was essential for lactation. In mothers depleted of the reserve of lactation promoting substance, the young responded to wheat germ oil.

Mason[56,58] showed that a transfer of vitamin E occurs across the placental barrier. Concentration of vitamin E in the placenta and the uterus of high vitamin E mothers is 5 times that of a full-term fetus.[56,57] On stock diets made deficient in vitamin E, he showed that degeneration of the testes of rats should occur in the same length of time, but that if the young were suckled by high vitamin E mothers, a delay in the degeneration of the testes from 20 to 40 days indicated that mammary transfer had occurred.

In humans, Shute[92] showed an increased output of milk in 35% of cases where lactation was poor upon adding wheat germ oil to diet. Sixty per cent were able to nurse longer than 3 months.

Effect on Male Reproductive System. Vitamin E deprivation in male animals brings about a response which differs from that in the female, in that the changes occurring in the male are irreversible; that is, they are not alleviated or relieved by administration of wheat germ oil or by other sources of vitamin E. This has been explained by the fact that in the male the damage is to the animal's own tissues, in contrast to the female, where the damage is to the fetal tissue.

Male fowl on vitamin E free diets for 1 year showed normal fertility of sperm.[9] By the end of the 2d year, 2 males were sterile. Sperm smear showed that structural changes occurred shortly after the commencement of the experiment. One showed testicular atrophy, and 3 showed degenerative changes. Mature sperm degenerate first and gradually degeneration proceeds to the outside of the seminiferous tubules.

Mason[56] and Marchesi[53] showed that diets deficient in vitamin E, but adequate in the other vitamins, have produced definite histologic injury to rat testes. Deficiency in vitamin A has produced testes degeneration not influenced by vitamin E. The histologic changes due to vitamin E deficiency in male testes are: (*a*) chromolysis and fusion of mature spermatozoa; (*b*) removal through the rete testis to the epididymis; (*c*) nuclear change and liquefaction of spermatids and secondary spermatocytes, and segregation of chromatin to form a crescent. Abnormal cells fuse into multinucleate masses; (*d*) Sertoli tissue shows no degenerative change though the nuclei have been irregular and syncytium more fibrous. Kudr-

jaschow[48d] says that the Sertoli nuclei exhibit structural changes which he thinks are related to disturbance of nutritive function. It takes roughly 50 days for the degeneration process to reach completion. There was no evidence produced to show regenerative capacity on the part of the seminiferous tubules. Forty gm. of lettuce a day had no curative effect. Other findings in male organs were discoloration of the seminal vesicles and decrease in weight of the testes and the prostate.

DiBassi[28d] examined human testes from 165 patients dying of sudden death. Of these, 44 showed multinucleate giant cells derived from spermatids, histologically similar to the picture of vitamin E deficient rat testis. Also on milk diets, male rats became sterile and showed the same histologic picture. However, females on the same diet produced living young, so changes in germinal epithelium cannot be attributable solely to vitamin E deficiency.[111]

A loss of interest in the female fowl by the male was noticed by one observer.[44] Others have claimed that these changes in sex behavior were not due to loss of vitamin E because they were not reversible when vitamin E was provided in the diets. Adamstone[9] says that the loss of sex interest on the part of the male fowl appears before any marked degeneration of the testis and before secondary sex characters show regression.

Distribution in Body Tissues. Cuthbertson[26] showed that vitamin E was stored in adipose tissue only when diet was unusually high in it. No storage took place in any other tissue. Moore[64,65] showed spectroscopically that it was only deposited in depot fat. Mason[58c] has assayed the vitamin E in the tissues of 338 rats which received either 4, 100, or 10,000 times the minimal daily requirement of vitamin E. He found that on the low intake the heart, lungs, and spleen contained almost twice as much vitamin E per gram of fresh tissue as the musculature, body fat and other vital organs; the liver had the least. On moderate intake of vitamin E, storage is augmented in the viscera, musculature and fat. The heart, lungs and spleen receive most of it. The liver's supply of vitamin E is increased 14 times, while the mammary gland concentrates twice as much as the liver. At the excessively high levels of vitamin E intake, the liver has about 150 times the amount which it contains at lower levels, hence it is the most valuable guide to previous intake and storage. Only a small fraction of the total amount of vitamin E ingested is stored in the rat, which confirms the suggestion that tocopherols may not be effectively absorbed from the gut or are readily broken down in the body.

Theoretical Concepts of Mode of Action of Vitamin E. Since no one has produced evidence as to how vitamin E acts in the body, but little space will be given to theories. Adamstone[10] believes that normal cell division requires vitamin E and in vitamin E deficiency abnormal excessive division occurs. The first recorded speculation was that vitamin E played a rôle in the utilization of iron. This was exploded and rejected by Mattill.[59] Vogt-Møller[110] has called it a morphogenic hormone. Drummond and Underhill[29] think its fundamental rôle is in hormone balance. Adamstone[7] has already pointed out its relationship to anthracene substances. Shute[92] has the idea, that in humans at least, vitamin E holds estrogens in equilibrium during pregnancy, and that a vitamin E deficiency results in an excess of estrogen in the blood. Some think[44,54,55] that vitamin E consists of two fractions, already mentioned. Wright and Drummond[115] suggest that tocopherols are part of the enzyme oxido-reduction system in the body. Ridgeway[80] showed, however, that no oxidation products of alpha tocopherols are likely to take part in reversible oxidations in the body.

Clinical Considerations. INDICATIONS FOR USE. Definite proof for the value of vitamin E as a remedy for human sterility is manifestly difficult to secure. Many causes are associated with human sterility and, as we have pointed out, animal experiments indicated vitamin E is concerned with only one phase of the female reproductive process, namely, the blood supply and nutrition of the embryo; and in the male with the maintenance of testicular function. By analogy, an inadequate diet of vitamin E in the human male might be revealed by non-viability or even complete absence of sperm; in the female, by abortion—the physiologic counterpart of absorption in rats. Such analogies, however, are dangerous as they may imply too much or too little. All we can do is to point out certain facts where vitamin E has been used in treating pathologic conditions and the manner that is recommended for such use.

Habitual Abortion. Chances of a full-term pregnancy in untreated cases of habitual abortion are about 60% after 2 successive abortions and about 27% after 3; while after 4 abortions only 6% can hope to have a full-term delivery.[15] Shute[85] suggests this condition is caused by an excess of anti-proteolytic activity which damages the nutrition of the trophoblast.

Currie[23–25] reported 30 cases of habitual abortion in which 18 were carried to term, 3 to more than the 34th week, and 5 were carried over 5 months, all on wheat germ oil. In a second series of known habitual aborters, 23 out of 29 delivered at term and the remaining 6 were carried over 6 months, again on wheat germ oil.

Vogt-Møller[109] reported 20 cases in which no anatomic or physiologic abnormalities could explain the repeated abortions; 17 of these bore living children after treatment with wheat germ oil. In a second series of 52 cases of habitual abortion, 38 living young were born following treatment with wheat germ oil. He first tried wheat germ oil in sterile cows and next in 2 human subjects who had aborted 4 and 5 times respectively. These 2 women had normal term pregnancies.

Watson[113] and Tew[113a] reported success in a series of 34 out of 46 cases of habitual abortion, but no benefit was obtained in overcoming cases of sterility.

Shute[88] says that in the blood serum of aborting women, a deficiency of vitamin E has permitted estrogenic substance to acquire a dominant position. Resistance to proteolysis disappears when treated with vitamin E. Further, he has shown that the blood serum of rats on vitamin E free diets developed the ability to resist tryptic ferment, comparable to the blood serum of aborting women.[87] Oral administration of wheat germ oil overcame this resistance. He reported 72% success in treating habitual abortion by vitamin E.[87]

Threatened Abortion. Another indication for vitamin E therapy is in the treatment of threatened abortion. Silbernagel and Burt[93c] have recently reported a series of 140 cases treated in this manner. Their criteria for diagnosis was vaginal bleeding with or without crampy pains. They made comparative tests with various methods of therapy which included conservative measures of bed rest and sedation; progesterone; alpha tocopherol acetate alone, given intramuscularly; alpha tocopherol acetate intramuscularly and orally; alpha tocopherol acetate intramuscularly and natural tocopherol given orally; alpha tocopherol acetate orally only; and natural tocopherols orally alone. Their results indicate that alpha tocopherol acetate hypodermically plus natural tocopherols orally is the ideal regimen for treating threatened abortion, having 85% of their women go to term without losing the fetus. Oral natural tocopherol alone

and oral wheat germ oil alone gave good results in 42% and 33% respectively. Progesterone alone carried only 18% of the cases to term and alpha tocopherol acetate intramuscularly carried 20% through.

Senile Vaginitis. Shute[93] has reported success in using wheat germ oil to treat this condition, especially associated with excess of estrin and hypothyroidism.

Abruptio Placentæ. This lesion, in which the placenta separates prematurely, is said to occur in about 0.3% to 2.8% of pregnancies. Many cases are undoubtedly overlooked because the early symptoms are not recognized. The condition in the advanced stage resembles shock, with or without uterine bleeding. Uterine pain, rigidity and tenderness, and sacral backache are characteristic. The patient may die of hemorrhage or may abort a macerated fetus. Shute[85] showed that 78% of these patients had a deficiency in vitamin E, and by giving 12 drams of wheat germ oil in 24 hours, he completely abolished the symptoms.[89] Shute[93b] refers to cases of pre-abruptios (probably the same as McKelney's "miniature premature separations"), which he diagnoses by finding areas of uterine tenderness to palpation. He states they disappear, only to recur, and *always* at the same site in the uterine wall. With these pre-abruptios may go the signs of early toxemia. Shute states that these areas of tenderness are frequently overlooked or wrongly diagnosed, often as appendicitis, "baby kicking," adhesions, and so forth. He further believes this uterine tenderness is almost *always the first sign of vitamin E deficiency in human pregnancy*, and that "it is always relieved by prompt administration of vitamin E." Such cases always show a high blood estrogen level and such an assay is "*sine qua non*" for diagnosis. In his later work he believes the dose required increases as the pregnancy proceeds, therefore, enough vitamin E must be given to control the symptoms rather than using any standard dose.[93b] He believes that vitamin E acts to neutralize the excess estrogenic substance which resists the intrusion of placental villi into the uterine wall. It leaves open the interesting possibility that toxemias of pregnancy may be due to dietary deficiency.

Male Sterility. Moench[63] has recently suggested the use of vitamin E in treating male sterility. Shute[92] reported 1 case of testes atrophy that returned to potency after vitamin E therapy, and also a case of testicular descent on vitamin E therapy after pregnancy urine had failed to produce this result. This seems, however, to be contrary to the attempts in rats to reverse testicular damage by giving vitamin E. Biskind and Falk[16b] have treated 11 cases of infertility in the male with vitamin B_1 and vitamin E in combination, and reported definite improvement in the number, motility and morphology of sperm in these people. Of these men, 8 succeeded in begetting children after treatment.

Congenital Anomalies. Often spontaneous abortions are associated with developmental anomalies of the fetus. Byerly[19] and Macomber[50] suggested that vitamin E deficiency is a factor in producing fetal deformities. Neither Vogt-Møller,[109–110] nor Watson[113] and Tew[113a] have reported any gross fetal anomalies in infants whose mothers were carried to term with wheat germ oil. Shute,[92] however, reported 2 anomalous fetuses in 29 pregnancies where the mother had been so treated. Currie[23–25] found 1 child, in a series of 21 cases treated with wheat germ oil, which died due to a structural defect.

One may thus accept the fact that failure of wheat germ oil therapy in these above mentioned conditions may be due to inadequate dosage, idiosyncrasy, hypothyroidism, seasonal depletion of vitamin E, rancid oil or abortions due to other causes than vitamin E deficiency.

INFLUENCE ON LABOR. Shute[91] showed that wheat germ oil used up to the onset of labor in no case prolonged the onset. Even the attempt to stop labor by massive dosage during the first stage was not successful.

DOSE. Danforth[27] says more is needed by the male to prevent testes changes than by the female to prevent "resorption" of the fetus. Eppstein[38] points out that absorption of vitamin E from the gut varies, and its destruction in the gut or in the tissues may be excessive, thus causing deficiency.

Currie[23–25] used 3 minims of wheat germ oil daily (in capsules) until the onset of labor. Macomber[50] showed that 500 mg. of wheat germ oil per day in 20% lard did not protect 44% of experimental rats, but that 20 gm. of lettuce per day did protect on the same diet. Shute[85] says that it should be given until the antiproteolytic factor has disappeared from the serum and continue with a dosage that will keep the serum normally digestible. He used 12 drams in the first 24 hours and 1 dram per day thereafter.[85,89,90] Later,[93b] he says that the dose should be the amount necessary to control symptoms of "pre-abruption" and to continue the drug to term. Vogt-Møller's clinic used 2 to 3 gm. per day with no special precautions to preserve its potency.[90] Three to 6 mg. per day are usually recommended in the treatment of threatened abortion.

POTENCY. Shute[91] showed that wheat germ oil that is not kept cold will lose its potency and thus signs of threatened abortion will return. In bulk or capsule form the oil retains its potency no longer than 8 days. Alpha tocopherol became ineffective when given with cod-liver oil.[52] Others[77] maintain that it can be kept in sealed vacuum cans for years and still retain potency. The preparation used most often is fresh ether extracted oil.

IDIOSYNCRASY. No toxic effect has been noted on 6 drams per day for 6 months. However 5 patients treated for vaginitis with wheat germ oil were sensitized and developed urticaria.[93] Shute[90] also had 5 adults and 1 infant who developed flatulence, hot flashes, urticaria, and nausea and vomiting who had been treated with vitamin E.

Summary and Conclusions. The present status of vitamin E may be summarized as follows:

1. The active principle of vitamin E is a polycyclic compound of the sterol type that possesses certain physical and chemical properties. Statements as to how such compounds are synthesized and their sources in nature are readily found in the literature. The relationship of vitamin E to anthracene derivatives has been established.

2. Whether growth and development are aided or not by vitamin E remains controversial.

3. That vitamin E has close relations with the endocrine systems of the body has been established, but its exact rôle has not yet been made clear.

4. Manifestations of vitamin E deficiencies (especially in rats) are retarded development and/or resorption of the fetus, and specific degeneration of the testis in males. Changes are reversible in the female. In the male the evidence is both insufficient and contradictory.

5. The mechanisms involved remain theoretical.

6. The correct use of vitamin E in humans, as far as reproduction is concerned, still remains to be gleaned from the future. However, certain facts seem apparent. Abruptio placentæ, if diagnosed early by the signs mentioned, is amenable to treatment with vitamin E. "The best therapy for abruptio is prevention and that is now possible" (Shute[93b]). Likewise threatened abortion seems to respond favorably to vitamin E. The largest series of cases treated thus far are those of habitual abortion, and in these

the figures average 75% good results with vitamin E in some form or other. However, the difficulty in evaluating all such data is obvious—no controls are possible. We do not know whether the patient would abort this particular time even if wheat germ oil had not been used. Further the number of cases reported and studied are still too few to be of much value statistically. In the other pathologic conditions, reports are still fewer and too vague to have practical significance at this time. However, failure to substantiate such reports may well reside in the technical difficulty in preparing and preserving the potency of wheat germ oil, as has been pointed out.

Vitamin E therapy will probably never play the rôle that its fellow vitamins have played in other conditions. It should, however, be studied much further, experimentally and clinically in the pathologic conditions mentioned, especially as no other valuable or specific therapeutic measures exist, as it apparently does no harm and has the possibility of doing good. When the number of well-studied cases is sufficient to be statistically imposing, its true worth may be better evaluated. "It is easily possible that in stressing the relation of the tocopherols to reproduction we may be missing their basic function—growth of the fetus and maintenance of male germinal epithelium perhaps being but a small part of the whole."[114]

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RADIOLOGY

UNDER THE CHARGE OF
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THE PRESENT STATUS OF CONTRAST MYELOGRAPHY

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CONTRAST myelography consists of the use of some type of medium which when injected into the spinal subarachnoid space allows the roentgenologic visualization of that space. By this procedure the presence of intraspinal tumors and other pathologic processes which obstruct, distort or obliterate the subarachnoid space can be detected.

The intraspinal use of such an agent was suggested first by Dandy[12] in 1919 when he predicted that tumors of the spinal cord might be localized by the injection of air. The actual intraspinal use of air to detect and localize tumors causing complete block was reported by Dandy[13] in 1925. However, in 1922 Sicard and Forestier[35] had described the intraspinal injection of iodized oil for the roentgenologic visualization of obstructing intraspinal tumors and this method was received with much enthusiasm. Air myelography was more or less abandoned. Odin, Runström and Lindblom[30] in 1929, and Camp[8] in 1930 recommended the use of iodized oil to detect unobstructing lesions of the spinal canal. Iodized oil myelography became a well-known and generally accepted method for the diagnosis of intraspinal tumors when neurologic localization was unsatisfactory. This type of iodized oil we shall refer to by its trade name, lipiodol, to distinguish it from iodized oil of different character which has been developed recently.

In 1934 Coggeshall and von Storch[11] used air to visualize the lower part of the dural sac in 3 normal persons and suggested that by this method "deformities of the contour of the dural sac may be seen as they are produced by neoplasms, congenital deformities, or traumatic lesions." In the same year Van Wagenen[36] demonstrated the level of 3 cord tumors with block by the use of air. Thus, interest in air myelography began to develop again. In 1937 Reichert,[32] and Scott and Young[34] reported the roentgenologic visualization of protruded intervertebral disks by air myelography.

There is little doubt that lipiodol was found to be most accurate in the visualization of intraspinal tumors. Camp and Addington[9] in 1939 reported the results of lipiodol myelography in 417 cases. Discounting 5 cases in which there was a lesion below an anomalous cul-de-sac, they found lipiodol to be accurate in detecting and localizing the lesion in 96.8% of the cases. They also described 13 cases in which operation was performed and which had been considered negative after lipiodol myelography. This included the 5 cases in which there was anomaly of the cul-de-sac and in which protruded lumbosacral disks were found. In 2 of the remaining 8 cases there were protruded lumbosacral disks, in 4 thickened ligamentum flavum was found, and in 2 no lesion was found at operation. This report of surgical findings in cases considered negative by myelography is most important. Almost all of the papers which have appeared in the literature regarding myelography deal only with the

surgical findings in cases considered positive by myelography. The erroneous impression that may result from this type of analysis is obvious.

There have been other statements with regard to the accuracy of lipiodol which agree fundamentally with those of Camp and Addington. Hampton found lipiodol to be accurate in 93% of 133 cases. Bell and Spurling[2] recommended lipiodol, as did Mixter[25] who warned that it must not be used promiscuously.

Camp[8] also has shown that with the use of lipiodol it is possible in many instances to determine whether a tumor of the spinal cord is extradural or intradural, and in the latter case whether the tumor is extramedullary or intramedullary. This is most important information if the tumor is a true neoplasm. He was able to identify the character of the lesion in 90.8% of his cases. It thus seems that for the accurate localization and gross identification of neoplasms of the spinal canal at any level lipiodol is the most trustworthy agent yet found.

There is some controversy as to the amount of oil necessary for diagnosis. There are many, for example Bell and Spurling, who feel that 2 cc. of lipiodol is sufficient. Others, for example Hampton, use a larger amount, usually about 5 cc. Camp[8] advised that 5 cc. be used since, in his opinion, with this amount small lesions are less likely to be missed than with a smaller amount, there is less danger of pseudo-arrests which simulate partially obstructing lesions, and the lipiodol does not break up so readily into globules in the thoracic and cervical regions.

With the larger quantity of lipiodol multiple tumors are found more easily, according to Camp.[7] Of 72 cases of tumors of the cord he found that 4% had multiple tumors. For this reason he emphasized that enough lipiodol must be used to allow examination of the entire canal. He expressed the opinion that 5 cc. is in reality no more irritating than 2 cc. and there is as much medico-legal objection to the small amount as there is to the larger amount. It should also be kept in mind that in a few days or weeks after injection the column of lipiodol breaks up more easily into globules and therefore the examination is most satisfactory immediately after the injection.

Since lipiodol was received with such enthusiasm at first and since its accuracy has been proved, there must be some reason for the further search for another agent to supplant it in contrast myelography. At first lipiodol was used too freely and rather promiscuously. Reactions were reported as the result of its irritating effect. There has been a great deal of experimental and clinical work in this respect and this has been well reviewed by Brown and Carr,[5] Marcovich, Walker and Jessico,[24] and Garland.[15] There is no doubt that there is often an immediate reaction within 24 hours after the injection. This may consist of any or all of the following: headache, fever, nausea, vomiting and stiff neck. The spinal fluid shows slight or moderate pleocytosis. Marcovich and his associates stated that these symptoms are gone within 72 hours. Love and Walsh[22] reported this early reaction and said: "We have seen no clinical reaction to iodized oil that might not have been produced by a spinal or cisternal puncture with the withdrawal of spinal fluid alone."

Camp[8] and Hampton[17] have warned that only fresh lipiodol may be used safely. At times aggravation of the patient's symptoms occurs after the injection of lipiodol but that also occurs when only a spinal puncture is done.

It is generally accepted now that a definite contraindication to the use of lipiodol is the presence of an inflammatory process involving the cord, brain or meninges.

So far as the delayed effect of lipiodol is concerned there is more controversy. Much of the experimental work done on animals would indicate that there results chronic arachnoiditis at least. There are some reports of actual damage to the cord. It seems that in many of these experiments on animals relatively larger quantities of lipiodol were used than are ever used for human patients. It also would seem that in some of the experiments the chronic arachnoiditis described might be due partially to the surgical procedures used in the experiments rather than being entirely ascribable to the lipiodol. In the majority of instances in which patients were followed for many months or several years after the injection little definite evidence could be found to indicate disability due to the presence of the lipiodol. Adson[1] has observed infrequently a symptom which, in his opinion, is due to residual lipiodol. That is sacral pain when the patient is standing. This pain is relieved when the lipiodol is removed.

Many of the cases reported which do show detrimental effect are cases in which the injection was made in the presence of an inflammatory process, or in which chronic arachnoiditis was present when the oil was injected. It does appear that when there is preëxisting chronic arachnoiditis this process is made worse by the permanent presence of lipiodol. On the other hand, Marcovich and his associates[24] mentioned that in some cases in which arachnoiditis develops after lipiodol myelography followed by operation, the arachnoiditis may be the result of bleeding which occurred during or after the operation rather than of the lipiodol. They concluded that "although the changes in the spinal cord and its membrane in animals after intrathecal injection of iodized oil are fairly severe, the constant pathologic changes—a slight proliferation of the arachnoid membrane with a few fine dural adhesions—in the human spinal cord following the injection of iodized oil are minimal. Constant parenchymal changes are not present."

Lipiodol remains permanently unless it is removed promptly after its injection. Within a relatively short period it begins to extend along the nerve sheaths in the lumbar and sacral regions. This part of the lipiodol is fixed in the tissues but most of the oil remains free in the arachnoid sac unless the membranes have been opened during operation, in which case some of the lipiodol escapes into the epidural tissues where it becomes fixed. As the result of free movement of the lipiodol in the subarachnoid space Garland, as well as Marcovich and his associates, reported droplets of oil in the basal cisterns. Garland's cases showed some fixation of the oil there while in the cases of Marcovich the oil was free. In none were there any resulting symptoms.

The fact that lipiodol remains permanently is one of the greatest objections to its use. This has been well stated by Camp,[8] ". . . . the history of many patients suffering from conditions of the back is complicated by injuries and insurance or medico-legal entanglements . . . . Resourceful attorneys and malingering patients may use roentgenograms which reveal the shadow of the remaining oil as a tangible basis for claiming aggravation of symptoms and such roentgenograms may have a profound effect on a sympathetic jury."

To overcome this objection there have been endeavors to remove lipiodol immediately after the examination. In 1936 Lucherini[22] first attempted to do this with some success. Later Adson[1] and Briesen[4] reported methods for the removal of lipiodol. Perhaps the most successful method has been that of Kubik and Hampton.[21] Briefly, this consists of the gentle aspiration of the lipiodol through a large needle. This has been used by others with considerable success. However, it is quite time-

consuming, many times it is not completely successful, and sometimes it is quite unsatisfactory. The complete removal of the lipiodol is usually not possible when the dura is opened during operation, although many times much of the oil can be removed. It does happen at times that lipiodol is injected accidentally into the epidural space. This has been studied by Hamby[16] who found that factors which tend to reduce the spinal fluid pressure, especially previous spinal puncture or air myelography, predispose to misplacement of lipiodol. Lipiodol which has been injected epidurally cannot be removed.

Thus we find that lipiodol yields very accurate results, it allows the examination of the entire canal, the roentgenoscopic examination can be repeated later if desired, and it will not only localize the lesion but many times will suggest the type of lesion present. On the other hand, lipiodol may cause some irritation of the meninges, its removal is difficult, and the medico-legal aspects of its use must always be considered.

The value of lipiodol in the diagnosis of true neoplasms of the spinal canal cannot be denied, but there has been discovered a different type of lesion of the spinal canal which has stimulated the attempt to replace lipiodol with some other medium. This mass, whose importance has been recognized only in the last several years, is the protruded intervertebral disk. According to Love and Walsh,[22] 96% of protruded intervertebral disks are found in the lumbar region and of these by far the greater part occur at the last two lumbar interspaces; 90% according to Scott and Young.[34] It is chiefly for this type of lesion that the use of air or oxygen myelography has developed. Air has also been used to define the level in cases of complete spinal block.

Ordinarily, however, air myelography visualizes only the lumbar region and is of no value above the 10th dorsal segment unless there is a block above this segment, according to Camp.[8] As he has stated, there are certain advantages to its use: "(1) there is no contraindication; (2) the air or oxygen is absorbed after the examination; (3) there is no irritating effect from the injection other than that resulting temporarily from the injection; (4) roentgenoscopic examination is not necessary and since the findings are recorded on roentgenograms these may be studied at the examiner's convenience." Camp has enumerated the following disadvantages: "(1) the procedure is unsatisfactory for non-obstructing lesions above the level of the conus medullaris; (2) the shadows produced with air and defects revealed by it are less distinct than those observed when iodized oil is used, their interpretation is correspondingly more difficult and unless the examiner is experienced in the procedure the likelihood of error is greatly increased; (3) the roentgenoscopic verification of any defect is not possible; (4) inconclusive results of examination are much more frequent when air is used than when iodized oil is used; (5) experience has shown the results of studies made with air (especially when such results are negative) are less accurate than the results obtained with iodized oil."

There are many who feel that the method with air is quite reliable. Chamberlain and Young[10] reported 300 cases and "in every case in which operation was performed the level of the lesion predicted after myelography examination was verified at laminectomy. Air studies have not been misleading as there were no instances in which the myelograms indicated a lesion without verification at operation." Poppen[31] also considered air myelography quite reliable and reported 175 cases in which the diagnosis of protruded disk was made and in 150 of which the diagnosis was confirmed at operation. It was Poppen who first used oxygen instead of air in

myelography. Oxygen is more rapidly absorbed than air and therefore there is less distress after its use. Oxygen is now used instead of air very frequently. Scott and Young also reported favorably for the use of air myelography. However, in none of these series has there been a report of the results of operation in those cases considered negative by air myelography. Camp[8] found air to be 83% accurate in those in which there were positive myelographic findings and in which operation was performed. However, he found that of those patients on whom operation was performed despite a negative finding by air myelography 77% had lesions. Hampton estimated that air will permit diagnosis of only about 50% of disks. He stated, "Air myelography is of distinct value when the findings are unequivocally positive, but it is of little value when the findings are equivocal or negative."

There is no question that air myelography has definite value but it is most important that its limitations be understood clearly. In cases of suspected protruded intervertebral disk a thorough understanding of the symptoms and neurologic signs associated with that condition is most essential. That aspect of the diagnosis is of greater importance than the roentgenologic examination. Camp and Addington[9] have shown that low backache with sciatica occurs in a fairly high percentage of cases in which there are tumors of the cervical or thoracic portion of the spinal cord. Therefore low backache and sciatica alone are not enough to justify the diagnosis of protruded lumbar intervertebral disk nor to warrant air myelography. The promiscuous use of air myelography for patients who have not had the proper thorough clinical and neurologic work-up is most dangerous and thus many patients may be submitted to unnecessary and therefore harmful surgical intervention.

Bradford and Spurling[3] have stated that "although the presence of a spinal neoplasm is unequivocally an indication for surgical removal when possible, the presence of posterior herniation of the nucleus pulposus is not an indication for surgical removal unless it has produced incapacitating radicular symptoms." This statement has been supported by the work of Horwitz[19] who has found, through anatomic studies, the following asymptomatic conditions simulating protruded disks at myelography: (1) posterior bulging of the entire intervertebral disk without localized herniation is a common finding in adult cadaver material; (2) degeneration of the intervertebral disk with subsequent narrowing of the intervertebral space may be associated with a settling of the upper vertebral body downward and backward on the vertebral body below, so that the postero-inferior surface of the vertebral body and the overlying disk material project posteriorly into the neural canal. This "posterior displacement" may be exaggerated by bony proliferation of this postero-inferior margin; (3) apparent bulging of the ligamentum flavum of normal thickness as result of marginal bony proliferation of the underlying facets of the apophyseal joints.

These false deformities apply both to lipiodol myelography and to air myelography but this is especially to be remembered with regard to air myelography since that method is being used so freely in the diagnosis of protruded intervertebral disk.

As has been suggested by many investigators and undoubtedly applied in many instances, it appears most logical and if after a complete clinical and neurologic examination a protruded intervertebral disk in the lumbar region is suspected air myelography should be used. If a definite deformity is found at a level that is in keeping with the neurologic findings, then

the diagnosis of protruded disk at that level can be made. As a matter of fact, slight deformities which appear in the air myelogram can be given a limited significance if these deformities are compatible with the neurologic findings. If, however, the findings in the air myelograms are not definite or not exactly compatible with the neurologic findings, lipiodol myelography should be employed. This applies also if the air myelogram is negative and the clinical picture is suggestive of a protruded disk.

It must be accepted, as shown by Hampton and Robinson,[18] that even with the use of lipiodol there may be a protrusion of the intervertebral disk at the 5th lumbar interspace which will produce a minimal defect or none in the lipiodol column. Anomalies of the cul-de-sac as described by Camp and Addington[9] will make the diagnosis of protruded lumbosacral disk impossible by myelography. It has been shown that protrusion of the intervertebral disk may be intermittent and if myelography is performed when the disk is not protruding the myelogram will, naturally, fail to show the lesion. Thus, we must accept the fact that protrusion of the intervertebral disk can occur without myelographic evidence. This emphasizes the importance of the clinical and neurologic examination.

Dandy[14] recently has advocated the abolition of all contrast myelography in the diagnosis of protruded intervertebral disk. In many places now, in cases in which the clinical picture is typical and clear-cut, these patients are being operated on without preliminary myelography and with excellent results. It seems that this is applicable only to typical cases and there are many cases which are not quite typical in certain respects but in which the patients are found by myelography to have protruded disks and obtain relief by surgical intervention. Dandy opposed myelography because he said that small disks and "concealed disks" are not seen at that examination. We must frankly acknowledge that no method of contrast myelography is always correct, and if the clinical and neurologic picture is quite typical and exact, then surgical exploration is indicated. This has been done in many cases, as reported by Camp, but this does not discount the value of myelographic confirmation in questionable cases.

In 1934 Lucherini[23] described thorotrast myelography. In 1938 in this country Nosik and Mortensen[29] reported using 4 cc. of a 25% solution of thorium dioxide. Later, papers appeared by Nichols,[25] Bunts,[6] and Nichols and Nosik.[27] There is no doubt that a most excellent visualization of the lumbar subarachnoid space is obtained in this manner. Thorotrast is miscible with the spinal fluid and gives a clear-cut outline, even showing each nerve sheath almost perfectly. Nosik[28] in 1943 reported his results with this medium. His positive diagnoses were found to be 93.7% correct. There was found to be 11.1% error when the myelographic diagnosis was negative. The thorotrast is removed by forced spinal drainage, using the method of Kubie and Retan.[20] Ten to 15% of the thorotrast remains as a rule and this amount is considered by the Council on Pharmacy and Chemistry of the American Medical Association not to have sufficient radioactivity to produce deleterious effects and to be too feeble to have physiologic significance.

Even if one is to accept as a fact this contention that the residual thorotrast is absolutely harmless, there is a greater objection to this medium, and that is the effect of accidental epidural injection of the solution. Epidural injection occurs occasionally with lipiodol and with air. One must expect it to happen with thorotrast at times. Thorotrast is extremely irritating to the tissues and after such an accident it cannot be removed. Certainly the medico-legal aspect of such an occurrence cannot

be minimized. Another objection to thorotrast is that only the lumbar segments and many times only the lower 3 lumbar segments are visualized. With thorotrast defects cannot be checked by roentgenoscopy, since it casts too faint a shadow to be seen in that manner. Forced spinal drainage causes distress and is a troublesome procedure.

Sanford and Doub[33] have devised a method, called epidurography, whereby air is injected into the epidural space in the lumbar region. In this way the localized protrusion of the disk is well shown in the lateral view. The main objection to this procedure is the technical difficulty, which is greater than with other methods of myelography. There may also be danger in injecting air into the vascular bed of the epidural space. The method is of use only in the lumbar region and only for protruded intervertebral disks.

Quite recently a new contrast medium called "Pantopaque" has been introduced. As yet there have been no reports as to its diagnostic value. However, a limited experience with its use may allow one to suggest some of its probable possibilities and limitations. This material is an iodized oil which is lighter than lipiodol. Since the weight and viscosity are less than those of lipiodol it can be aspirated from the arachnoid sac more easily and quite rapidly. By using a reasonable amount of care most of the pantopaque can be aspirated from the sac immediately after the examination, using the needle through which it was injected. It is said that the material which remains after aspiration gradually becomes less opaque until finally it is no longer visible roentgenographically. Pantopaque in the lumbar region resembles lipiodol. The shadow cast is similar to that produced by lipiodol and the material is manipulated in a manner similar to lipiodol. Roentgenoscopic as well as roentgenographic examination is used.

The main disadvantage is that pantopaque is light and not very viscid. For that reason small defects may be missed and false defects may be produced. Because of the low viscosity the material breaks up into globules very easily after it gets above the conus medullaris. This may make the examination of the dorsal and cervical regions less satisfactory. It would appear, after very limited experience with pantopaque, that it may be an improvement over air myelography for the examination of the lumbar region but may not be completely satisfactory for the examination of the canal above the lumbar region.

Conclusions. 1. A completely satisfactory medium for contrast myelography has not yet been discovered.

2. For accurate examination of the entire spinal canal, lipiodol remains the most satisfactory agent. There are objections to its promiscuous use, however.

3. Air myelography has limited but definite value, mostly for the examination of the lumbar region to detect protruded intervertebral disks.

4. The clinical and neurologic picture is most important in the diagnosis of protruded intervertebral disk. Contrast myelography has value only when the findings are compatible with the clinical and neurologic impression.

5. "Pantopaque" is a useful contrast agent; but its value cannot yet be determined because of insufficient experience with it.

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BOOK REVIEWS AND NOTICES

NUTRITION AND CHEMICAL GROWTH IN CHILDHOOD. Vol. I, Evaluation. By ICIE G. MACY, PH.D., Director of the Research Laboratory of the Children's Fund of Michigan. Pp. 432; 66 figs. Springfield, Ill.: Charles C Thomas, 1942. Price, $5.00.

THE Reviewer regrets that it is not possible to do justice to this isolated first volume of the complete monograph on the work of Dr. Macy Hoobler and her associates of The Children's Fund of Michigan. Careful study of this book makes it evident that the whole project was more comprehensive than even the numerous individual papers which have appeared in the past decade indicated. This contribution to the literature is so notable that the Reviewer undertakes the analysis with hesitation, fearing lest he underestimate its value.

Furthermore a complete evaluation of the project and the data must depend not only upon the present book, but also on the second volume yet to be published.

The present volume presents the outline and organization of the project, the methods utilized to secure data together with their mathematical treatment, a critique of this and all research projects concerned with chemical and metabolic balance studies, and finally representative data selected from all aspects of the work illustrative of results and relationships. In short this work represents the most complete, the most meticulous and probably the most thoroughly reliable study of biochemical growth in childhood.

Naturally it was fortunate that there was available an organization such as the adjacent Methodist Children's Village in which the subjects to be studied could live under conditions approximating home life and at the same time provide assurance that food and fluid intakes would be controlled and all specimens collected according to plan.

The investigation of nutrition and chemical growth individual included study of the intake, utilization and excretion of 18 chemical substances by children taken to be as normal as the most reliable selective methods could determine them. Eleven children aged 4 to 10 years were studied first over a period of 95 days; 4 years later 11 subjects aged 55 to 104 months were investigated for 225 days, and 4 years later 7 of the same subjects were again restudied for 55 days. (It is most unfortunate that previous reviews have indicated that the studies were carried out on 29 *separate* individuals, thus failing to emphasize the serial study of the same children, which enhances the value of the whole contribution.)

Although the balance studies comprise the major portion of the work presented here, there are also numerous studies of the physiologic, including roentgenologic, and chemical aspects of digestion and excretion. Energy metabolism is presented in relation to protein, fat, carbohydrate and to the requirements for normal growth.

There is an interesting and significant chapter on the several chemical elements of the blood with partition between serum, plasma and cells. The studies on the cells are particularly stimulating since this field promises to be fruitful of research in the growth and metabolism of living mammalian cells, of which blood cells may be taken as fairly representative.

The chemical methods used are given in detail; those selected for these studies being the most practical and yet the most precise. To facilitate the completion of quantitative determinations as numerous as were required in this project, and to ensure greater coördination of results of administrative procedures, the polorograph and the spectograph were used. The utilization of the polorograph in research of this type is succinctly outlined. These sections are most valuable and will be used for future reference.

There is a brief but adequate section concerned with the methods of compilation and mathematical treatment of the experimental data with significant examples.

A fairly complete and entirely satisfactory bibliography of the literature of related research and this page index are accurate and adequate.

Dr. Macy and her associates are to be congratulated and one awaits with interest the publication of the second volume since the complete monograph is a great accumulation of facts and will be indispensable to pediatricians and investigators alike. E. T.

THE SONNETS OF SHAKESPEARE. A Psycho-Sexual Analysis. By H. McCLURE YOUNG. Pp. 121. Copyrighted 1937 by H. McClure Young, 217 Exchange National Bank Bldg., Columbia, Mo. Price, $2.00.

THIS is an interesting, critical analysis of the thesis that the *Sonnets* express the poet's reaction to a love triangle that developed between him, his mistress, and his patron, Henry Wriothesly, Earl of Southampton. It is assumed that these *Sonnets* are numbered in the same orderly sequences in which they were written, and that thus they can be dated between 1596 and 1603, and the identity of the young man of the first series and his escape from execution be established. No light is thrown "on the identity of the Dark Lady, and but little on that of the Rival Poet and the affable familiar ghost." The study throws more light, if the author's plausible deductions are correct, on textual meaning and on Shakespeare's personality than on psycho-sexual problems. The booklet is recommended more to those interested in borderline medico-literary topics than to students of psychiatry. E. K.

AN ATLAS OF ANATOMY. VOL. I. UPPER LIMB, ABDOMEN, PERINEUM, PELVIS, LOWER LIMB. By J. C. BOILEAU GRANT, M.C., M.D., CH.B., F.R.C.S. (EDIN.), Professor of Anatomy, University of Toronto. Pp. 214; 227 illus. Baltimore: The Williams & Wilkins Company, 1943. Price, $5.00.

THIS is the first volume of a projected 2-volume atlas of human anatomy. The half-tone illustrations are of dissections and line drawings, both types having color added where emphasis was indicated. Many of the views selected for illustration are similar to those seen by students in the course of classroom dissection, the illustrations being, in general, of regions rather than systems. The drawings were obviously made by a skilled artist, with gratifying attention to accuracy. For classroom use it is unfortunate that the arrangement on the page of some plates necessitates turning the book sideways. No regular descriptive text accompanies the plates. However, on each page the author has with appropriate brief observations and comments directed the reader's attention to salient points. The Birmingham revision of the nomenclature is used throughout, but where this differs substantially from the BNA both terms are given. There is a freshness of viewpoint about this atlas which makes it a fitting companion volume for the author's previously published textbook. In this Reviewer's opinion it will occupy an important place among books readily available for students of anatomy, whether they be in the classroom or in practice. R. W.

DOCTOR PRYOR: AN AUTOBIOGRAPHY. By DR. J. W. PRYOR. Pp. 312; 17 illus. Cynthiana, Ky.: The Hobson Press, 1943. Price, $3.00.

ALMOST all successful physicians have had full lives that have included much of human interest. Relatively few, however, can extract from their experiences a narrative that deserves to appear in print. Biographies are, with extremely few exceptions, more instructive and more revealing than autobiographies.

This autobiography, to the Reviewer, holds a mid-position and is worth printing as a simple, honest presentation of the life of a simple honest medical teacher and practitioner that has influenced many others toward the good, and is typical of thousands of the better physicians of this country. It is not surprising that a distinct cross-sectional view of medical life in the Mississippi Valley through the latter part of its formative period emerges. We may hope, then, with the author that it will interest and inspire many, though in a different way from the great accounts of great figures such as those of Pasteur and Osler.

The offset style of type has good readability and comeliness and is highly appropriate for a wartime publication. There are fewer than the average number of typographical errors. E. K.

A Synopsis of Clinical Syphilis. By James Kirby Howles, B.S., M.D., M.S., Professor of Dermatology and Syphilology, and Director of the Department, Louisiana State University School of Medicine; Senior Visiting Physician, Charity Hospital of Louisiana at New Orleans; Visiting Physician, French Hospital, Mercy Hospital, Hotel Dieu, Southern Baptist Hospital and Touro Infirmary. Pp. 671; 121 illus., 2 color plates: St. Louis: C. V. Mosby Company, 1943. Price, $6.00.

As the flood of compends on various subjects continues unabated, it is necessary, in fairness to the authors, that these volumes be considered individually from the standpoint of an attempt to condense masses of material into a small space rather than as more complete treatment of the subject. Viewed from this angle, Dr. Howles' "Synopsis of Clinical Syphilis" can be taken as a handy, conservative, usually impersonal discussion of syphilology with a working bibliography, concise chapter summaries and adequate differential lists.

The illustrations are generally good but have a tendency to emphasize unintentionally, of course, the erroneous belief that syphilis is chiefly a disease of negroes (*J. Am. Med. Assn.*, **122**, 365, 764, 1943). This peculiarity of Dr. Howles' book is obviously due to the locus of his practice (Charity Hospital, New Orleans). Casual performance of serologic tests in the doctor's office is poor syphilologic practice, yet on page 149 the author recommends the Johns modification of the Meinicke-Butler test for office use. On page 281 and page 285 is a detailed description of syphilis of the hair and scalp but no mention of alopecia associated with neurosyphilis. Although there is a section on latent or asymptomatic syphilis, there is no adequate stress on the increasing number of patients who are apparently asymptomatic (symptomless) from the very inception of their infection.

This book, except for the limitations demanded by brevity, may be evaluated as a fair discussion of clinical syphilis. H. B.

Clinical Parasitology. By Charles F. Craig, M.D., M.A. (Hon.), F.A.C.S., F.A.C.P., Col., U. S. Army (Retired), D.S.M., Emeritus Professor of Tropical Medicine in The Tulane University of Louisiana, New Orleans; and Ernest C. Faust, M.A., Ph.D., Professor of Parasitology in the Department of Tropical Medicine, The Tulane University of Louisiana. Third ed. Pp. 767; 284 illus., 4 colored plates. Philadelphia: Lea & Febiger, 1943. Price, $9.00.

The third edition of this very useful text is entirely comparable in excellence to the two earlier ones. Four full-page colored plates, which illustrate the morphology of the organisms of malaria in thin and thick blood smears and the additions to the section of Arthropod parasites, greatly increase its value. It may be said again that the book is certainly the equal of any in the field. H. R.

NEW BOOKS

Fundamental Exercises for Physical Fitness. By CLAIRE COLESTOCK, A.B., M.A., Assistant Director of Physical Education, City Schools, Pasadena, Calif.; and CHARLES LEROY LOWMAN, M.D., F.A.C.S., Chief of Staff, Orthopædic Hospital, Los Angeles, Calif. Pp. 314; 72 figs. New York: A. S. Barnes & Co., 1943.

Nervousness, Indigestion, and Pain. By WALTER C. ALVAREZ, M.D., Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant in the Division of Medicine, The Mayo Clinic, Rochester, Minn. Pp. 488. New York: Paul B. Hoeber, Inc., 1943. Price, $5.00.

Reaction to Injury. Pathology for Students of Disease Based on the Functional and Morphological Responses of Tissues to Injurious Agents. By WILEY D. FORBUS, M.D., Professor of Pathology, Duke University and Pathologist to the Duke Hospital. Pp. 797; 532 illus. (20 in color). Baltimore: The Williams & Wilkins Company, 1943. Price, $9.00.

Doctor in the Making. The Art of Being a Medical Student. By ARTHUR W. HAM, M.B., Associate Professor of Anatomy, in Charge of Histology, Faculty of Medicine, University of Toronto; Honorary Secretary of the Banting Research Foundation; and M. D. SALTER, M.A., PH.D., Lecturer and Research Fellow in the Department of Psychology, Faculty of Medicine, University of Toronto. Illustrations by JEAN MCCONNELL. Pp. 179. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $2.00.

Victories of Army Medicine. Scientific Accomplishments of the Medical Department of the United States Army. By EDGAR ERSKINE HUME, Colonel, Medical Corps, United States Army. Pp. 250; 2 plates (1 in color). Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $3.00.

Convulsive Seizures. How to Deal with Them. A Manual for Patients, Their Families and Friends. By TRACY J. PUTNAM, M.D., Professor of Neurology and Neurosurgery, College of Physicians and Surgeons, Columbia University; Director of Services of Neurology and Neurosurgery, Neurological Institute of New York. Pp. 169; 12 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $2.00.

Medical Clinics on Bone Diseases. A Text and Atlas. By I. SNAPPER, M.D., Formerly Professor of Medicine, Peiping Union Medical College, Peiping, China. Pp. 225; 30 plates. New York: Interscience Publishers, Inc., 1943. Price, $10.75.

Treatment of Experimental Data. By ARCHIE G. WORTHING, University of Pittsburgh; and JOSEPH GEFFNER, Weirton Steel Company. Pp. 342; 13 tables; many figs. New York: John Wiley & Sons, Inc., 1943. Price, $4.50.

Essentials of Proctology. By HARRY E. BACON, B.S., M.D., F.A.C.S., F.A.P.S., Professor and Head of the Department of Proctology, Temple University Medical School and Hospital; Head of Department of Proctology, St. Mary's Hospital; Consulting Proctologist, Rush Hospital, National Stomach Hospital, Douglass Hospital, Mercy Hospital and Paul Kimball Hospital, Lakewood, N. J.; Fellow, International College of Surgeons. Introduction by CURTICE ROSSER, B.A., M.D., F.A.C.S., F.A.P.A., Professor of Proctology, Baylor University, Dallas, Texas. Pp. 345; 168 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $3.50.

Hypertension. By IRVINE H. PAGE, A.B., M.D., Director, Lilly Clinic, Indianapolis City Hospital. Pp. 80; 7 figs. Springfield, Ill.: Charles C Thomas, 1943. Price, $1.50.

Medical Clinics of North America. Symposium on Specific Methods of Treatment. Boston Number. Pp. 245. Philadelphia and London: W. B. Saunders Company, 1943. Price, $16.00 per year.

Biochemistry of the Fatty Acids and Their Compounds, the Lipids. By W. R. Bloor, Professor of Biochemistry and Pharmacology, The University of Rochester, Rochester, N. Y. American Chemical Society Monograph Series. Pp. 386; tables and charts. New York: Reinhold Publ. Corp., 1945. Price, $6.00.

Handbook of Tropical Medicine. By Alfred C. Reed, M.D., Associate Clinical Professor of Medicine, Stanford University School of Medicine; and J. C. Geiger, M.D., Director of Public Health, San Francisco, Calif. Pp. 188. Stanford University, Calif.: Stanford University Press, 1943. Price, $1.50.

Atlas of Orthopedic Pathology. By D. M. Angevine, Major, Medical Corps, A.U. S., and J. E. Ash, Colonel, Medical Corps, U. S. A., Curator. Prepared at the Army Medical Museum, Office of the Surgeon-General, U. S. Army from material in the Registry of Orthopedic Pathology. Sponsored by the American Academy of Orthopedic Surgeons and the American Board of Orthopedic Surgery, 1943. Pp. 91; many plates. Washington, D. C. Price, $5.00. Requests should be addressed to The Curator, Army Medical Museum, Washington 25, D. C.

Proceedings of the Rudolf Virchow Medical Society in the City of New York. Vol. I. Edited by the Publication Committee, Franz M. Groedel, M.D., and Bruno Kisch, M.D. Pp. 76 (1942). Published by Brooklyn Medical Press, Inc., New York (1943). Price, $1.00.

This new periodical contains 35 articles on miscellaneous subjects, mostly by ex-Germans, that were contributed to the 1942 meetings of the Virchow Society, formerly the Deutscher medizinischer Leseverein von New York. E. K.

Synopsis of Tropical Medicine. By Sir Philip Manson-Bahr, C.M.G., D.S.O., M.D., F.R.C.P., Senior Physician to the Hospital for Tropical Diseases, Royal Albert Dock and Tilbury Hospitals; Consulting Physician in Tropical Diseases to the Dreadnought Seamen's Hospital, London; Director, Division of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine; Consulting Physician to the Colonial Office and Crown Agents for the Colonies; Consultant in Tropical Medicine to the Admiralty and to the Royal Air Force, etc. Pp. 224; 5 plates. Baltimore: The Williams & Wilkins Company, 1943. Price, $2.50.

Microscopic Technique in Biology and Medicine. By E. V. Cowdry, Professor of Anatomy, Washington University, and Director of Research, The Barnard Free Skin and Cancer Hospital. Pp. 206. Baltimore: The Williams & Wilkins Company, 1943. Price, $4.00.

NEW EDITIONS

Biochemistry for Medical Students. By William Veale Thorpe, M.A. (Cantab.), Ph.D. (Lond.), Reader in Chemical Physiology, University of Birmingham. Third ed. Pp. 476; 39 illus. Baltimore: The Williams & Wilkins Company, 1943. Price, $4.50.

An Introduction to Medical Mycology. By George M. Lewis, M.D., Member of the American Dermatological Association, Inc.; Fellow of the American College of Physicians, of the American Medical Association and of the New York Academy of Medicine; Member of the New York Dermatological Society and of the Manhattan Dermatological Society; Associate Attending Physician (Dermatology), The New York Hospital; Assistant Professor of Clinical Medicine (Dermatology), Cornell University Medical School; Attending Dermatologist to St. Clare's Hospital; Visiting Dermatologist to Welfare Hospital, etc.; and Mary E. Hopper, M.S., Research Fellow in Medicine, Cornell University Medical School. Second ed. Pp. 342; 77 plates (1 in color). Chicago: The Year Book Publishers, Inc., 1943. Price, $6.50.

The Compleat Pediatrician. By W. C. DAVISON, Professor of Pediatrics, Duke University School of Medicine, Formerly Acting Pediatrician in Charge, The Johns Hopkins Hospital. Fourth ed. Durham, N. C.: Printed by Seeman Printery for Duke University Press, 1943. Price, $3.75 by check or $4.00 on credit.

Physiology of the Nervous System. By JOHN FARQUHAR FULTON, M.A., D.PHIL., D.Sc. (OXON.), S.B., M.D. (HARV.), Sterling Professor of Physiology, Yale University, Formerly Fellow of Magdalen College, Oxford. Second ed. Pp. 614; 111 figs. London, New York, Toronto: Oxford University Press, 1943. Price, $9.00.

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